10/03/93

SEARCH REQUEST FORM

ACS DB# _____

9/9 06p

9/9 80

9/10 57

Scientific and Technical Information Center

SEP 05

Requester's Full Name: JANE ZARA Examiner #: 77512 Date: 9/5/03

Art Unit: 1635 Phone Number 306-5820 Serial Number: 09/716,320

Mail Box and Bldg/Room Location: 1D03 Results Format Preferred (circle): PAPER DISK E-MAIL

If more than one search is submitted, please prioritize searches in order of need.

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Please provide a detailed statement of the search topic, and describe as specifically as possible the subject matter to be searched. Include the elected species or structures, keywords, synonyms, acronyms, and registry numbers, and combine with the concept or utility of the invention. Define any terms that may have a special meaning. Give examples or relevant citations, authors, etc, if known. Please attach a copy of the cover sheet, pertinent claims, and abstract.

Title of Invention: Reducing Radiation / Drug Resistance in cells.

Inventors (please provide full names): Chang, E.

Earliest Priority Filing Date: 11/21/00

For Sequence Searches Only Please include all pertinent information (parent, child, divisional, or issued patent numbers) along with the appropriate serial number.

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STIC Search Report
Biotech-Chem Library

STIC Database Tracking Number:103193

TO: Jane Zara
Location: CM1/11D03&11E12
Art Unit: 1635
Friday, September 12, 2003

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DB=USPT,PGPB,JPAB,EPAB,DWPI,TDBD; PLUR=NO; OP=OR			
L4	L3 and l1	30	L4
L3	(radiation with resistance) or (drug with resistance)	30306	L3
L2	L1 same (radiation or drug) same resistance	2	L2
L1	her2 same (antisense or ribozyme$)	129	L1

END OF SEARCH HISTORY

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  File 155:MEDLINE(R)  1966-2002/Nov W3
*File 155: For updating information please see Help News155. Alert
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removal, customized scheduling. See HELP ALERT.

      Set  Items  Description
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? s neu or her (w) 2 or erbb?3 and (antisens? or ribozym?)
           7239  NEU
          71431  HER
        5270316  2
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             60  ERBB?3
          36120  ANTISENS?
           6254  RIBOZYM?
      S1    8030  NEU OR HER (W) 2 OR ERBB?3 AND (ANTISENS? OR RIBOZYM?)
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           8030  S1
       19954705  PY<1997
      S2    3783  S1 AND PY<1997
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         775216  RESIST?
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...completed examining records
      S4      67  RD (unique items)
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 4/3,AB/1     (Item 1 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09243249   97126553   PMID: 8971468
  Metastatic breast cancer.
  Kennedy M J
  Johns Hopkins Oncology Center, Medical Oncology, Baltimore, MD
21287-8936, USA.
  Current opinion in oncology (UNITED STATES)  Nov 1996, 8 (6)
 p485-90, ISSN 1040-8746  Journal Code: 9007265
  Document type: Journal Article; Review; Review, Tutorial
  Languages: ENGLISH
  Main Citation Owner: NLM
  Record type: Completed
  The management of metastatic breast cancer continues to provide enormous
challenges. The taxanes have significant activity in patients with
resistant disease, and combination regimens are being evaluated as
first-line therapy. The combination of paclitaxel and doxorubicin appears
to have substantial activity, but troublesome cardiac toxicity has been
noted in a recently reported study. Docetaxel has been shown to be very
active in initial phase II evaluation, notably in women with anthracycline-
resistant disease. The controversy over high-dose therapy continues,
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and its role in the management of metastatic breast cancer outside the confines of clinical trials remains unclear. The **HER-2** protein appears to be a predictive factor for patients with metastatic disease. Antibody therapy directed at this target can produce responses in a proportion of patients. Bisphosphonates appear to be beneficial to patients with lytic bony metastases when administered in conjunction with cytotoxic or hormonal therapy.

4/3,AB/2 (Item 2 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09164451 97075205 PMID: 8917631
Heregulin induces increase in sensitivity of an erbB-2-overexpressing breast cancer cell type to lysis by lymphokine-activated killer cells.
Cardillo M; Yankelevich B; Mazumder A; Lupu R
Vincent T. Lombardi Cancer Center, Georgetown University, Washington, DC 20007, USA.
Cancer immunology, immunotherapy : CII (GERMANY) Sep **1996**, 43 (1) p19-25, ISSN 0340-7004 Journal Code: 8605732
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
The erbB-2 oncoprotein is overexpressed in 30% of tumors from breast and ovarian cancer patients and it is related to poor overall and disease-free survival. In vitro studies on erbB-2-overexpressing cells have found a strong correlation between this oncogene overexpression and relative **resistance** to lymphokine-activated killer (LAK) cell lysis. gp30/heregulin/NDF (**neu** differentiation factor), indirect activators of erbB-2, are able to induce a more differentiated phenotype on erbB-2-overexpressing, erbB-3- and/or erbB-4-positive breast cancer cells. We tested the ability of these highly homologous growth factors to stimulate LAK cell lysis of breast cancer cells. Our experiments demonstrated a marked increase in LAK cell cytotoxicity towards an erbB-2-overexpressing, erbB-3-positive cell line by treatment of these cells with heregulin for 72 h. In contrast we did not observe any enhancement of lysis of MCF-7, a cell line that does not overexpress erbB-2 and is positive for the erbB-3 and erbB-4 receptors, after treatment with heregulin. The increased lysis was associated with upregulation of intercellular adhesion molecule 1 (ICAM-1), down-regulation of erbB-2 and increased binding between breast cancer cells and LAK cells. Pre incubation of target (SKBR3) cells with blocking anti-ICAM-1 antibody completely abrogated the enhanced cytotoxicity. A similar effect was observed by pretreatment of the effector (LAK) cells with antibodies directed against LFA-1, the receptor for ICAM-1. These results suggest the possible utilization of gp30/heregulin in the treatment of breast cancer patients by its ability to stimulate patient immune responses.

4/3,AB/3 (Item 3 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09051474 96404529 PMID: 8808711
Overexpression of c-erbB-2/**neu** in breast cancer cells confers increased **resistance** to Taxol via mdr-1-independent mechanisms.
Yu D; Liu B; Tan M; Li J; Wang S S; Hung M C
Department of Surgical Oncology, The University of Texas MD Anderson Cancer Center, Houston 77030, USA.
Oncogene (ENGLAND) Sep 19 **1996**, 13 (6) p1359-65, ISSN 0950-9232 Journal Code: 8711562
Contract/Grant No.: CA58880; CA; NCI; CA60488; CA; NCI; CA60856; CA; NCI
Document type: Journal Article
Languages: ENGLISH

Main Citation Owner: NLM
Record type: Completed
It has been reported that breast tumors that overexpress c-erbB-2/**neu** are less responsive to certain adjuvant chemotherapy regimens than those that express a normal amount of the gene product. To investigate whether overexpression of the c-erbB-2/**neu**-encoded p185 can indeed lead to increased chemoresistance in breast cancers, we introduced the human c-erbB-2/**neu** gene into the very low p185-expressing MDA-MB435 human breast cancer cells and examined Taxol sensitivities among the parental MDA-MB-435 cells and stable transfectants which express increased levels of p185. The p185-overexpressing MDA-MB-435 transfectants were more **resistant** to Taxol than the parental cells. The increased Taxol **resistance** was not accompanied by changes in doubling time and S-phase fraction. The increased Taxol **resistance** was independent from oncogenic transformation since it was observed only in c-erbB-2/**neu** -transformed cells and not ras-transformed cells when oncogene-transformed NIH3T3 cells were examined. To study whether p185 induced Taxol **resistance** through the mdr-1 pathway, we examined the mdr-1-encoded p170 levels in these transfectants. The MDA-MB-435 cells expressed very low levels of p170 and there was no increase of p170 expression in the p185-overexpressing MDA-MB-435 transfectants. Furthermore, these transfectants were not sensitized to Taxol treatment by mdr-1 blocker thioradazine. These data demonstrated that overexpression of c-erbB-2/**neu** can lead to intrinsic Taxol **resistance** independent from mdr-1 mechanisms.

4/3,AB/4 (Item 4 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

08883845 96242604 PMID: 8672868
Oncogenes and growth factors as indicators of carcinogen exposure.
Jussila T; Makinen M; Stenback F
Department of Pathology, University of Oulu, Finland.
Experimental and toxicologic pathology : official journal of the Gesellschaft fur Toxikologische Pathologie (GERMANY) Feb **1996**, 48 (2-3) p145-53, ISSN 0940-2993 Journal Code: 9208920
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
The occurrence of different components of the cell growth regulation pathway as expressed in experimental skin carcinogenesis in haired carcinogen-sensitive NMRI, in haired carcinogen **resistant** DBA/2 mice and in hairless SKH/1 mice was studied by morphological and immunohistochemical methods. The results were compared with respect to neoplastic response, number of tumors, tumor behaviour and to the inducing agent (UV irradiation or chemical carcinogen), in order to increase our understanding of specific alterations in neoplastic development caused by extraneous agents and to determine their possible usefulness as indicators of carcinogen exposure. The expression of growth factors (transforming growth factor alpha and epidermal growth factor), growth factor receptors (epidermal growth factor receptor/c-erbB-1 and c-erbB-2/**neu**), cell signalling component c-myc, the nuclear transcription factor Harvey-Ras and the tumor suppressor gene p53, were studied in carcinogen- and UV-induced tumor formation in mouse. The results showed increased oncogene expression as well as growth factor expression in the skin during tumor development appearing early in neoplastic and premalignant conditions and becoming more distinct during neoplastic progression. Efforts to delineate specifically initiated cells prior to the appearance of morphologically detectable alterations including dysplasia, papilloma formation and squamous cell carcinomas, were unsuccessful. Increased staining by antibodies to growth factors and oncogenes were also observed in DBA/2 animals **resistant** to tumor formation. It is concluded that oncogene expression and growth

factor protein deposits are associated with carcinogenic effects, partly explaining the mechanism of action of these agents, but the applicability, as such, for the analysis of potential hazardous agents needs further studies.

4/3,AB/5 (Item 5 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

08873609 96234384 PMID: 8640763
Enhancement of chemosensitivity by tyrphostin AG825 in high-p185(**neu**) expressing non-small cell lung cancer cells.
Tsai C M; Levitzki A; Wu L H; Chang K T; Cheng C C; Gazit A; Perng R P
Department of Medicine, School of Medicine, National Yang-Ming University, Taipei, Taiwan, Republic of China.
Cancer research (UNITED STATES) Mar 1 **1996**, 56 (5) p1068-74, ISSN 0008-5472 Journal Code: 2984705R
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
The **HER-2/neu** gene product, p185(**neu**), is a membrane-bound receptor with tyrosine kinase activity. High levels of p185(**neu**) is correlated with intrinsic chemoresistance of non-small cell lung cancer (NSCLC) cell lines. We investigated the effects of tyrphostin AG825, a selective tyrosine kinase inhibitor preferentially inhibiting **HER-2/neu** kinase, on the chemosensitivities and on the **drug** -induced cell cycle changes of NSCLC cell lines that expressed different levels of p185(**neu**). Compared to the low-p185(**neu**) expressing cell lines, we found that the high-p185(**neu**) expressing cell lines were more **resistant** to doxorubicin, etoposide, and cis-diamminedichloroplatinum(II) but more sensitive to AG825. AG825 was able to significantly enhance the chemosensitivities of the high-p185(**neu**) expressing cell lines, whereas it had little effect on the chemosensitivities of the low-p185(**neu**) expressing cells, with a few exceptions in which minor antagonistic effects were observed. Although high concentrations of AG825 could reduce the **drug**-induced G(2) arrest that was accompanied by the activation of phosphorylated p34(cdc2), we failed to find any remarkably differential effects of AG825 on **drug** -induced G(2), arrest and the accompanying phosphorylation status of p34(cdc2) of the high- and and the low-p185(**neu**) expressing cell lines. In summary, tyrphostin AG825 can enhance chemosensitivity in high- but not in low-p185(**neu**) expressing NSCLC cell lines. This differential effect cannot be explained by the alterations of **drug** -induced cell cycle changes by AG825. Our results provide a rationale to develop p185(**neu**)- specific tyrphostin and to test them in combination with anticancer agents in vivo and in clinical trials.

4/3,AB/6 (Item 6 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

08871840 96226092 PMID: 8637714
Sensitization of **HER-2/neu** -overexpressing non-small cell lung cancer cells to chemotherapeutic drugs by tyrosine kinase inhibitor emodin.
Zhang L; Hung M C
Department of Tumor Biology, University of Texas MD Anderson Cancer Center, Houston 77030, USA.
Oncogene (ENGLAND) Feb 1 **1996**, 12 (3) p571-6, ISSN 0950-9232 Journal Code: 8711562
Contract/Grant No.: CA 16672; CA; NCI; CA 58880; CA; NCI; CA 60856; CA; NCI
Document type: Journal Article

Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
Overexpression of the **HER-2/neu** proto-oncogene which encodes tyrosine kinase receptor p185neu, has been observed frequently in many human cancers, including non-small cell lung cancer (NSCLC), and is correlated with poor patient survival in these cancers. In addition, **HER-2/neu** overexpression in NSCLC is known to induce chemoresistance. Recently, we demonstrated that emodin, a tyrosine kinase inhibitor, suppresses **HER-2/neu** tyrosine kinase activity in **HER-2/neu** -overexpressing breast cancer cells and preferentially represses proliferation of these cells. The work described here was carried out to examine (1) whether the tyrosine kinase activity of p185neu is required for **resistance** to chemotherapeutic drugs of **HER-2/neu** -overexpressing NSCLC cells and (2) whether the tyrosine kinase inhibitor emodin can sensitize these cells to chemotherapeutic drugs. We found that emodin decreased tyrosine phosphorylation of **HER-2/neu** and preferentially suppressed proliferation of **HER-2/neu** -overexpressing NSCLC cells. Furthermore, the combination of emodin with cisplatin, doxorubicin or etoposide (VP16) synergistically inhibited the proliferation of **HER-2/neu** -overexpressing lung cancer cells, whereas low doses of emodin, cisplatin, doxorubicin, or VP16 alone had only minimal antiproliferative effects on these cells. These results indicate that tyrosine kinase activity is required for the chemoresistant phenotype of **HER-2/neu** -overexpressing NSCLC cells and that tyrosine kinase inhibitors such as emodin can sensitize these cells to chemotherapeutic drugs. The results may have important implications in chemotherapy for **HER-2/neu**-overexpressing cancers.

4/3,AB/7 (Item 7 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

08856691 96208584 PMID: 8646686
In vitro modulation of tumor progression-associated properties of hormone refractory prostate carcinoma cell lines by cytokines.
Sokoloff M H; Tso C L; Kaboo R; Taneja S; Pang S; deKernion J B; Belldegrun A S
Immunotherapy Laboratory, Prostate Cancer Program, Division of Urology, Department of Surgery, UCLA School of Medicine, Los Angeles, California 90024, USA.
Cancer (UNITED STATES) May 1 **1996**, 77 (9) p1862-72, ISSN 0008-543X Journal Code: 0374236
Contract/Grant No.: CA-16024; CA; NCI
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
BACKGROUND: Cytokines exert cytostatic and immunomodulatory effects on carcinoma cells. Growth inhibition of human prostate carcinoma by cytokines has been demonstrated both in vitro and in vivo, whereas the cellular and molecular changes in prostate carcinoma properties after cytokine treatment have never been characterized. We have thus investigated whether the intrinsic properties of prostate carcinoma cells that are associated with tumor development and progression can be altered by direct cytokine treatment. METHODS: LNCaP, DU-145, and PC-3 cell lines were treated with tumor necrosis factor-alpha (TNF-alpha) (200 U/mL), interferon-gamma (IFN-gamma) (500 U/mL), human leukocyte interferon (IFN-alpha) (500 U/mL), and interleukin-2 (IL-2) (400 U/mL). The expression of (prostate-specific antigen [PSA] and prostate-specific membrane [PSM]), androgen receptor (AR), growth factors, oncogenes, collagenase, cell adhesion molecules, HLA antigens, cell adhesion to human bone marrow stroma, and cell growth were determined by quantitative polymerase chain reaction (PCR) analysis,

fluorescence-activated cell sorter (FACS) analysis, and cell attachment and proliferation assays, and were compared with non-treated cells. RESULTS: PCR analysis indicated that only LNCaP cells expressed PSA, PSM, and AR mRNA. Cytokine treatment did not alter PSM mRNA expression, whereas a 15-fold decrease in PSA and a 5-fold reduction in AR mRNA expression was detected in TNF-alpha-treated cells. The down regulation of PSA production was also demonstrated at the protein level in a dose-dependent fashion. A fivefold decrease in PSA mRNA was also detected in IL-2-treated LNCaP cells but without a reduction in AR. Down regulated epidermal growth factor receptor (EGF-R) and basic fibroblast growth factor (b-FGF) mRNA expressions were detected in TNF-alpha- and IFN-alpha-treated DU-145 and PC-3 cells, whereas, only reduced EGF-R expression was observed in LNCaP cells. IFN-gamma and IL-2 treatment down regulated the expression of collagenase Type IV mRNA in DU-145 and PC-3 cells, whereas tumor transforming growth factor-beta (TGF-beta) and IL-6 mRNA expressions did not exhibit any essential changes after cytokine treatment. A reduction in c-myc mRNA expression was observed in TNF-alpha- and IFN-alpha-treated cells, whereas no change in **HER-2** expression was noted in any cytokine treated cells. Up regulated P-cadherin, but not E-cadherin, mRNA expression was detected in TNF-alpha- and IFN-gamma-treated PC-3 cells. FACS analysis revealed that all but IL-2-treated cells had enhanced HLA Class I expression, with the maximum effect seen in TNF-alpha-treated LNCaP cells (threefold increase). Up regulated HLA Class II expression was seen only in IFN-gamma-treated cells. All cytokine-treated DU-145 and PC-3 cells expressed reduced levels of alpha3, but not beta1, integrin. Up regulated of ICAM-1 expression was seen in all cytokine treated DU-145 and PC-3 cells, whereas no change in CD44 occurred. Cytokine treatment reduced the binding affinity of LNCaP and DU-145, but not of PC-3 cells, to human bone marrow stromal cells, and all cytokines but IL-2 showed a mild to moderate growth inhibition to prostate cancer cells, with a marked inhibition only observed in TNF-alpha-treated LNCaP cells. CONCLUSIONS: Cytokine treatment can effectively alter several prostate carcinoma properties that are closely associated with tumor invasion and a metastatic phenotype, suggesting that immunotherapy via the local delivery of cytokines may have a potentially therapeutic role in the treatment of hormone-refractory prostate cancer through both direct and indirect antitumor mechanisms.

4/3,AB/8 (Item 8 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

08795324 96124899 PMID: 8548764
Correlations between intrinsic chemoresistance and **HER-2/neu** gene expression, p53 gene mutations, and cell proliferation characteristics in non-small cell lung cancer cell lines.
Tsai C M; Chang K T; Wu L H; Chen J Y; Gazdar A F; Mitsudomi T; Chen M H; Perng R P
Department of Medicine, Medical College, National Yang-Ming University, Taiwan, Republic of China.
Cancer research (UNITED STATES) Jan 1 **1996**, 56 (1) p206-9, ISSN 0008-5472 Journal Code: 2984705R
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
Using a panel of 20 non-small cell lung cancer (NSCLC) cell lines established from previously untreated patients, we investigated the relationships between intrinsic chemoresistance (to four agents used commonly in the therapy of NSCLC) and **HER-2/neu** gene expression (which encodes glycoprotein p185neu), p53 gene mutations, and cell proliferation characteristics. Our results demonstrated that high p185neu expression was correlated with chemoresistance, low S-phase fractions, and long doubling times. By contrast, cell lines expressing relatively low levels of p185neu were relatively chemosensitive and had

higher S-phase fractions and shorter doubling times. Although mutation of the p53 gene was a common event in this panel of cell lines (present in 18 of 20 lines), there was no relationship between mutations at any specific codon and chemoresistance or cell proliferation characteristics. Multivariate analysis revealed that the level of p185neu was the only independent predictor for chemoresistance to doxorubicin, etoposide, and probably cisplatin. Although intrinsic chemoresistance almost certainly is a multifactorial process, overexpression of p185neu may be an important factor in the chemoresistance of NSCLC.

4/3,AB/9 (Item 9 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

08792650 96128880 PMID: 8596130
Expression of the multidrug-**resistance** (MDR) gene in breast cancer.
Correnti M; Cavazza M E; Guedez N; Herrera O; Suarez-Chacon N R
Instituto de Oncologia y Hematologia, M.S.A.S., Caracas, Venezuela.
Journal of chemotherapy (Florence, Italy) (ITALY) Oct **1995**, 7 (5) p449-51, ISSN 1120-009X Journal Code: 8907348
Document type: Clinical Trial; Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed

Of the approximately 18,000 new cases of cancer in Venezuela each year, only half can be treated with surgery and radiation. The remainder must be treated systematically using chemotherapy or biological response modifiers. It has become evident that any **drug resistant** human tumors express the MDR1 gene, since MDR1 RNA levels are elevated in many cancers that do not respond to chemotherapy. Human mammary carcinomas have multiple oncogene alterations, the most frequently reported being overexpression of the oncogenes c-myc, int-2, **neu** and c-myb. Thirteen specimens of mammary cancer were obtained by biopsy of untreated patients in stage IIIB. All these patients received three cycles of FAC or CMF-L+GM-CSF after biopsy. In the slot blot analysis of RNA from invasive carcinomas, MDR1 and c-myc transcripts were detectable at a high level in 30% of tumors. Two patients with increased levels of MDR1 before chemotherapy did not respond to the treatment and distant metastasis and death occurred in these patients. Another patient, MDR1-negative before therapy, did not respond to CMF-1 + GM-CSF and showed high levels of MDR1 transcripts in a second biopsy which was obtained during surgery.

4/3,AB/10 (Item 10 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

08776120 96132679 PMID: 8541224
SKOV3 ovarian carcinoma cells have functional estrogen receptor but are growth-**resistant** to estrogen and antiestrogens.
Hua W; Christianson T; Rougeot C; Rochefort H; Clinton G M
Department of Molecular and Medical Genetics, Oregon Health Sciences University, Portland 97201, USA.
Journal of steroid biochemistry and molecular biology (ENGLAND) Dec **1995**, 55 (3-4) p279-89, ISSN 0960-0760 Journal Code: 9015483
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed

Estrogen receptor positive ovarian cancer is often refractile to antiestrogen therapy. Here we describe the SKOV3 human ovarian carcinoma cell line as an in vitro model for estrogen and antiestrogen **resistant** ovarian cancer. While SKOV3 cells expressed estrogen receptor (ER) mRNA and protein at a similar level as the estrogen responsive T47D breast carcinoma cell line, their growth was not responsive

to estradiol (E2) and was not inhibited by the antiestrogens OH-tamoxifen and ICI 164,384. The ER in SKOV3 cells was normal with respect to apparent Kd for binding with E2, E2 regulation of a transiently transfected ERE driven reporter gene, and E2 stimulation of expression of the early growth response genes c-myc and c-fos. However, the SKOV3 cells exhibited no expression of the progesterone receptor gene (PR) even after addition of E2, and the protein products of the estrogen responsive genes **HER-2/neu** and cathepsin D were expressed at constitutive levels that were not regulated by E2. Therefore, estrogen **resistance** in these cells may be a result of constitutive expression and loss of E2 regulation of selected growth regulatory gene products rather than a defect in estrogen activation of ER as a transcriptional regulator.

4/3,AB/11 (Item 11 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

08771866 96121776 PMID: 7501643
Occurrence of N-acetyl- and N-O-diacetyl-neuraminic acid derivatives in wild and mutant Crithidia fasciculata.
Matta M A; Aleksitch V; Angluster J; Alviano C S; De Souza W; Andrade A F ; Esteves M J
Laboratorio de Ultra-estrutura Celular (DUBC), Instituto Oswaldo Cruz, Fundacao Oswaldo Cruz, Rio de Janeiro, Brazil.
Parasitology research (GERMANY) **1995**, 81 (5) p426-33, ISSN 0932-0113 Journal Code: 8703571
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
The cell-surface expression of sialic acids in wild-type Crithidia fasciculata and three **drug-resistant** mutants (FU(R)11, TR3, and TFRR1) was analyzed using fluorescein-labeled Limulus polyphemus agglutinin (LPA) binding, glycosidase of known sugar specificity, and thin-layer chromatography (TLC). Gas-liquid chromatography-mass spectrometry (GC-MS) analysis using both electron-impact (EI-MS) and chemical ionization (CI-MS) by isobutane with selected ion monitoring (SIM) was also used. The surface location of sialic acid was inferred from LPA binding to whole cells abrogated by previous treatment with neuraminidase. An exception occurred with the TFRR1 strain, which after incubation with neuraminidase showed increased reactivity with the fluorescent lectin. Both N-acetyl- and N-O-diacetyl-neuraminic acids were identified in the flagellates by TLC, with a clear predominance being noted for the former derivative. However, the content of N-O-diacetyl-neuraminic acid was preferentially found in the TFRR1 strain. The GC-MS analysis of the acidic component of the TFRR1 mutant strain confirmed the occurrence of N-acetyl-neuraminic acid (Neu5Ac) by the presence of the diagnostic ions (m/z values: 684 and 594 for CI-MS and 478, 298, and 317 for EI-MS) and also by comparison with the standard Neu5Ac retention time. GC-MS analysis also showed fragments (m/z values: 654 and 564 for CI-MS and 594, 478, 298, and 317 for EI-MS) expected for the 7-O- and 9-O-acetyl-N-acetyl-neuraminic acids (Neu5,7Ac2 and **Neu** 5,9Ac2, respectively).

4/3,AB/12 (Item 12 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

08771683 96121866 PMID: 7495981
Interaction between erbB-receptors and heregulin in breast cancer tumor progression and **drug resistance**.
Lupu R; Cardillo M; Harris L; Hijazi M; Rosenberg K
Vincent T. Lombardi Cancer Research Center, Georgetown University School of Medicine, Lombardi Cancer Research Center S-122, Washington, DC 20007, USA.

Seminars in cancer biology (UNITED STATES) Jun **1995**, 6 (3) p135-45, ISSN 1044-579X Journal Code: 9010218
Document type: Journal Article; Review; Review, Tutorial
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed

The type I growth factor receptor family is increasingly recognized as important in the development and maintenance of breast cancer. The family currently consists of four closely related members: the epidermal growth factor receptor (EGF-R/erbB-1), erbB-2, erbB-3 and erbB-4. Putative ligands which bind directly to or indirectly activate erbB-2/3/4 have been characterized recently. This still growing family of EGF-related growth factors includes gp30, its homolog heregulin (HRG), the rat homolog **neu** differentiation factor (NDF), glial growth factors (GLIA), ARIA and a 50 kDa factor from COLO 16 cells. The understanding of the function, biology and interactions of these growth factor receptors and their ligands will have far-reaching implications for the prognosis and treatment of breast cancer. This review focuses on advances and future directions for further investigations intended to clarify the mechanism and significance of erbB/ligand interactions in breast cancer.

4/3,AB/13 (Item 13 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

08630721 95389574 PMID: 7660512
Reversion of human prostate tumorigenic growth by azatyrosine.
Benoit R M; Eiseman J; Jacobs S C; Kyprianou N
Department of Surgery, University of Maryland School of Medicine, Baltimore, USA.
Urology (UNITED STATES) Sep **1995**, 46 (3) p370-7, ISSN 0090-4295 Journal Code: 0366151
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed

OBJECTIVES. Azatyrosine, an antibiotic isolated from a Streptomyces species, has been previously shown to have antitumor activity against ras- and **neu** -transformed fibroblasts and human epithelial cells. In this study, we investigated the effect of azatyrosine on human prostate cancer cell growth and the reversion potential of this antibiotic on prostate tumorigenic cell lines. METHODS. Three androgen-independent human prostate cancer cell lines (TSU-Prl, DU-145, and PC-3) were cultured in the presence of azatyrosine and their growth rates were determined over a 7-day period. Following exhaustive treatment with azatyrosine for 5 weeks, three azatyrosine-**resistant** colonies were cloned from the PC-3 cell line and were subsequently established as stable cell lines. The growth characteristics of these azatyrosine-**resistant** clones were examined both in vitro and in vivo to establish their "potentially revertant" profiles. RESULTS. Incubation with azatyrosine (for 7 days) resulted in greater than 95% in vitro growth inhibition of the three parental prostate cancer cell lines. Analysis of the biologic properties of these azatyrosine-**resistant** cell lines revealed: (1) a significant reduction in in vitro growth rates; (2) a decreased rate of DNA synthesis as measured by thymidine uptake; and (3) a decreased ability for colony formation in soft agar. Moreover all three azatyrosine-**resistant** clones exhibited suppressed tumorigenicity in severe combined immunodeficient (SCID) mice when compared with the parental cell line. An important observation was that one revertant clone demonstrated complete loss of tumorigenicity. On the basis of this biologic behavior, these cell lines were characterized as revertants. Cytogenetic analysis revealed gross chromosomal differences between the revertant clones and the parental cell line. Northern hybridization analysis demonstrated elevated expression of the K-rev-1 and bcl-2 but not the rrg mRNA transcripts in the revertant

cell lines. CONCLUSIONS. These results suggest that azatyrosine inhibits prostate tumorigenic growth; it has a high reversion efficiency on human prostate cancer cells; and the K-rev-1 suppressor gene and the bcl-2 proto-oncogene could be potentially involved in the reversion mechanism mediated by azatyrosine. This reversion of prostate cancer cells to an apparently nontumorigenic phenotype points to a potentially significant therapeutic role for azatyrosine in the treatment of advanced prostate cancer.

4/3,AB/14 (Item 14 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

08615900 95372922 PMID: 7645018
Effects of oncogenes on the **resistance** to cis-diamminedichloroplatinum(II) and metallothionein gene expression.
Yamada-Okabe T; Yamada-Okabe H; Kashima Y; Doi R
Department of Hygiene, Yokohama City University, School of Medicine, Japan.
Toxicology and applied pharmacology (UNITED STATES) Aug **1995**, 133 (2) p233-8, ISSN 0041-008X Journal Code: 0416575
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
Transformation of NIH3T3 cells with the ras, the sis, or the **neu** oncogene rendered cells less susceptible to cis-diamminedichloroplatinum(II). Since **resistance** to cis-diamminedichloroplatinum(II) is reported to be associated with increased levels of metallothionein, we examined effects of these oncogenes on metallothionein gene expression. NIH3T3 cells were first transfected with the lacZ gene whose transcription is under the control of mouse metallothionein I promoter and then with the ras, the sis, or the **neu** oncogene. The ras and the sis oncogenes increased beta-galactosidase activities which were induced either by metal (cadmium and zinc) or by glucocorticoid (dexamethasone), whereas the **neu** oncogene repressed its activity. When SV40 early promoter was used instead of metallothionein I promoter for the lacZ gene transcription, the beta-galactosidase activities were not affected by metal, dexamethasone, or any of these oncogenes. This result was coincident with that of reverse transcription polymerase chain reaction that metal-induced MT I mRNA was only detected in the sis- or the ras-transformed cells, whereas any of these oncogenes did not affect the metal-induced transcription of the MT II gene. These results demonstrate that the ras and the sis oncogenes upregulate the metal- or glucocorticoid-induced transcription from metallothionein I promoter, but the **neu** oncogene negatively regulates it. Thus, **resistance** to the chemotherapeutic agent by oncogenic transformation is partly associated with the metallothionein gene expression, and MT I and MT II gene expressions are differently controlled by different oncogenes.

4/3,AB/15 (Item 15 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

08544302 95303514 PMID: 7784095
HER-2 tyrosine kinase pathway targets estrogen receptor and promotes hormone-independent growth in human breast cancer cells.
Pietras R J; Arboleda J; Reese D M; Wongvipat N; Pegram M D; Ramos L; Gorman C M; Parker M G; Sliwkowski M X; Slamon D J
UCLA School of Medicine, Department of Medicine 90095, USA.
Oncogene (ENGLAND) Jun 15 **1995**, 10 (12) p2435-46, ISSN 0950-9232 Journal Code: 8711562
Contract/Grant No.: P01 CA32737; CA; NCI; R01 CA36827; CA; NCI; R29 CA60835; CA; NCI

Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed

Growth of human breast cells is closely regulated by steroid hormone as well as peptide hormone receptors. Members of both receptor classes are important prognostic factors in human breast cancer. Clinical data indicate that overexpression of the **HER-2** gene is associated with an estrogen receptor-negative phenotype. In this study, we demonstrate that introduction of a **HER-2** cDNA, converting non-overexpressing breast cancer cells to those which overexpress this receptor, results in development of estrogen-independent growth which is insensitive to both estrogen and the antiestrogen, tamoxifen. Moreover, activation of the **HER-2** receptor in breast cancer cells by the peptide growth factor, heregulin, leads to direct and rapid phosphorylation of ER on tyrosine residues. This is followed by interaction between ER and the estrogen-response elements in the nucleus and production of an estrogen-induced protein, progesterone receptor. In addition, overexpression of **HER-2** receptor in estrogen-dependent tumor cells promotes ligand-independent down-regulation of ER and a delayed autoregulatory suppression of ER transcripts. These data demonstrate a direct link between these two receptor pathways and suggest one mechanism for development of endocrine **resistance** in human breast cancers.

4/3,AB/16 (Item 16 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

08513517 95271702 PMID: 7538595
Enhanced chemoresistance by elevation of p185neu levels in **HER-2/neu**-transfected human lung cancer cells.
Tsai C M; Yu D; Chang K T; Wu L H; Perng R P; Ibrahim N K; Hung M C
Chest Department, Veterans General Hospital-Taipei, Taiwan.
Journal of the National Cancer Institute (UNITED STATES) May 3 **1995**, 87 (9) p682-4, ISSN 0027-8874 Journal Code: 7503089
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed

4/3,AB/17 (Item 17 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

08484801 95243202 PMID: 7726141
CD31 quantitative immunocytochemical assays in breast carcinomas. Correlation with current prognostic factors.
Charpin C; Devictor B; Bergeret D; Andrac L; Boulat J; Horschowski N; Lavaut M N; Piana L
Department of Pathology, Centre Hospitalo-Universitaire Timone, Marseilles, France.
American journal of clinical pathology (UNITED STATES) Apr **1995**, 103 (4) p443-8, ISSN 0002-9173 Journal Code: 0370470
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed

The distribution of PECAM-1/CD31 molecule was investigated in 133 breast carcinomas using monoclonal antibody and frozen sections. Anti-CD31 labels endothelial cells and reflects stromal angiogenesis. The CD31 immunoreactivity was evaluated by computer-assisted analysis of digitized microscopic images. The automatic screening of the whole preparation and the measurements of the mean CD31 immunostained surface was performed in each case. A similar procedure was achieved for p53, cathepsin D, P-gp,

pHER-2/**neu** , Ki67, pS2 estrogen and progesterone antigenic sites immunodetection. The image analysis of positive CD31 surface was variable, ranging from 4% to 33% (mean 14.7%, SD = 5.43). The CD31 positive surface correlated (P < .01) with the Nottingham prognostic index, but not with the tumor size, the node status, the tumor grade, nor with the patient age. Also the CD31 immunoreactivity was independent of the pHER-2/**neu**, Ki67 antigen, p53, ER, PR and pS2 immunodetectable expression in tumors, but correlates with that of cathepsin D (P = .024) and P-gp (P = .028), which reflects the multi-**drug resistance** capacity of tumor cells. In conclusion, CD31 positive vessels assessed on frozen sections by image analysis constitute an excellent method of evaluating tumor stromal angiogenesis, and can be further used for clinical purposes. The results also suggest that the CD31/PECAM molecule may be involved in the spread of tumor by interacting with extracellular matrix lysis that results from the tumor cell proteasic activity and with multidrug **resistance**.

4/3,AB/18 (Item 18 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

08463688 95226253 PMID: 7710905
Role of gene amplification in **drug resistance**.
Schoenlein P V
Medical College of Georgia, Department of Cell and Molecular Biology, Augusta 30912.
Cancer treatment and research (NETHERLANDS) **1994**, 73 p167-200, ISSN 0927-3042 Journal Code: 8008541
Document type: Journal Article; Review; Review, Academic
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed

4/3,AB/19 (Item 19 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

08260957 95018325 PMID: 7932810
Quantitative immunocytochemical assays of P-glycoprotein in breast carcinomas: correlation to messenger RNA expression and to immunohistochemical prognostic indicators.
Charpin C; Vielh P; Duffaud F; Devictor B; Andrac L; Lavaut M N; Allasia C; Horschowski N; Piana L
Department of Pathology, Hopital de la Timone, Marseille, France.
Journal of the National Cancer Institute (UNITED STATES) Oct 19 **1994**, 86 (20) p1539-45, ISSN 0027-8874 Journal Code: 7503089
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
BACKGROUND: Chemotherapy failure that is due to cellular **drug resistance** remains a major problem in most cancer patients. One type of **drug resistance** that has been characterized is the multidrug **resistance** phenomenon, which demonstrates a reduced ability of cancer cells to accumulate drugs as a result of the effects of an energy-dependent unidirectional **drug** efflux pump with a broad substrate specificity. This **drug** pump is composed of a 170-kd transmembrane glycoprotein referred to as the P-glycoprotein (P-gp) that uses energy in the form of adenosine triphosphate to transport drugs through a channel formed by transmembrane segments. PURPOSE: Our purpose was to detect the levels of P-gp expression in frozen untreated breast carcinomas by immunocytochemical assays and to correlate these levels to current prognostic indicators and, in a few cases, to MDR1 (also known as PGY1) mRNA expression by polymerase chain reaction (PCR). METHODS: The immunocytochemical expression of the multidrug **resistance** gene, P-gp, was investigated using a specific

monoclonal antibody (JSB1) against P-gp in 5-microns frozen sequential sections of breast carcinomas obtained from 213 patients. Microscopic images of immunostained preparations were evaluated by image analysis and were compared with MDR1 transcription (mRNA) assessed by PCR in 16 patients. Quantitative P-gp immunocytochemical assays were correlated to histoprognostic factors and immunocytochemical indicators. RESULTS: Among the 213 breast carcinomas tested, 113 (53%) were P-gp positive, but in 28% of the tumors, the immunostained surface accounted for less than 5% of the total area stained. Quantitative immunocytochemistry reflecting the amount of intracellular P-gp antigen strongly correlated (r = 0.865; two-sided, P < .0001; Pearson's test) with the quantitative evaluation of the scanner analysis of mRNA transcripts. The P-gp expression was significantly (two-sided, P < .001) correlated with p53 expression in tumors, to cathepsin D and Ki67 (two-sided, P < .01) immunoreactivity, and to a lesser extent, the detection of estrogen receptor antigenic sites (two-sided, P = .019). P-gp expression was found to be independent of expression of progesterone receptor and pS2, pHER-2/**neu**, and CD31 in tumors and from patient age, tumor size, histologic types, grades and Nottingham prognostic index, and nodal status. CONCLUSIONS: The quantitative immunocytochemical assays of P-gp are correlated to PCR analysis of MDR1 expression, and such correlations can be useful in evaluating potential multidrug **resistance** in breast cancer. However, the clinical significance of P-gp immunodetections remains to be further determined.

4/3,AB/20 (Item 20 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

08257472 95014666 PMID: 7929529
Characterization of an established human, malignant, glioblastoma cell line (GBM) and its response to conventional drugs.
Perego P; Boiardi A; Carenini N; De Cesare M; Dolfini E; Roberto-Giardini ; Magnani I; Martignone S; Silvani A; Soranzo C; et al
Division of Experimental Oncology B, Istituto Nazionale per lo Studio e la Cura dei Tumori, Milan, Italy.
Journal of cancer research and clinical oncology (GERMANY) **1994**, 120 (10) p585-92, ISSN 0171-5216 Journal Code: 7902060
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
A cell line, GBM, was established from a human malignant glioblastoma and was characterized with particular reference to its response to conventional drugs. The GBM cell line exhibited a 73 +/- 7 h doubling time in monolayer cultures. Expression of glial fibrillary acidic and S-100 proteins was observed. Karyotype analysis of GBM cells at early passages revealed the presence of two near-triploid clones (A and B) with multiple chromosome rearrangements; a 100% frequency for clone B was observed in the established cell line. GBM cells had tumorigenic properties, since the s.c. injection of cultured cells into nude mice gave rise to slowly growing tumors. The morphology of GBM cells was retained during in vitro and in vivo passages, as judged by light microscopy. GBM cells were relatively **resistant** to most conventional drugs; among the tested drugs, only taxol exhibited a marked cytotoxic effect comparable to that found in cells of a different tumor type. GBM cells were found positive for the epidermal growth factor receptor, HER2-**neu** and P-glycoprotein by flow cytometry of cells labelled with monoclonal antibodies. In spite of the expression of relatively high gamma-glutamyltransferase activity, the intracellular glutathione level was comparable to that of other chemosensitive tumor cells. This glioblastoma cell line is a suitable model for the identification and preclinical studies of new agents and provides an additional system to explore the molecular basis of the intrinsic **drug resistance** of glioblastoma.

4/3,AB/21 (Item 21 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

08147082 94282713 PMID: 7912163
ERBB2 amplification is associated with tamoxifen **resistance** in steroid-receptor positive breast cancer.
Borg A; Baldetorp B; Ferno M; Killander D; Olsson H; Ryden S; Sigurdsson H
Department of Oncology, University Hospital, Lund, Sweden.
Cancer letters (IRELAND) Jun 30 **1994**, 81 (2) p137-44, ISSN 0304-3835 Journal Code: 7600053
Document type: Clinical Trial; Journal Article; Randomized Controlled Trial
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
Amplification and overexpression of the ERBB2 (**HER-2/neu**) oncogene has been implicated as contributing to the development of human breast cancer, and as a predictor of poor survival. In the present non-randomized study of 871 primary invasive breast tumours, ERBB2 activation was significantly correlated to a shorter disease-free and overall survival in the subgroup of patients receiving adjuvant tamoxifen therapy, but not in the untreated group. Further subcategorization demonstrated the relationship to poor prognosis to be confined to lymph node positive and steroid receptor-positive tumours. We suggest that steroid receptor and ERBB2-positive breast tumours are **resistant** to tamoxifen therapy and, supported by experimental evidence showing an oestrogen receptor dependent up-regulation of ERBB2 expression upon tamoxifen administration, possibly even growth stimulated by the **drug** .

4/3,AB/22 (Item 22 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

08139474 94273126 PMID: 8004612
Prognostic factors in early breast carcinoma.
Mansour E G; Ravdin P M; Dressler L
Cancer Care Center, Case Western Reserve University, Cleveland, Ohio.
Cancer (UNITED STATES) Jul 1 **1994**, 74 (1 Suppl) p381-400, ISSN 0008-543X Journal Code: 0374236
Document type: Journal Article; Review; Review, Academic
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
Several investigators, the SEER data, and the ECOG/Intergroup study have shown that patients with small tumors (< 0.5 cm) have a recurrence rate of less than 2%, compared to 20-25% for large tumors (> or = 5 cm). Nuclear grade and tumor differentiation are established indicators; however, the interobserver lack of concordance has thwarted their use in clinical trials. The presence of peritumoral lymphatic and blood vessel invasion (PLBI) is associated with a relative risk of recurrence of 4.7. The predictive value of the presence of hormone receptors in tumors is associated with a favorable disease free and overall survival difference of 8-10%; however, this advantage is being eroded by the early appearance of other factors, such as the epidermal growth factor receptor (EGFR), proliferative capacity (S-phase), nuclear grade, and **HER-2/neu** oncogene. Concordance among the different methods of hormone-receptor assay (immunocytochemical, sucrose gradient, and dextran-coated charcoal) is essential to refine the true value of these factors. DNA flow cytometry measurements of ploidy (DNA content) and S-phase fraction are the most characterized of the prognostic factors. There are conflicting reports regarding the clinical significance of ploidy

status, while measurements of S-phase fraction clearly indicate a robust association with disease free and overall survival. Our data continue to show that S-phase, but not ploidy, can predict time to recurrence significantly in untreated patients, even when data are stratified for tumor size. **HER-2/neu** oncogene is expressed in about 50% of ductal carcinoma in situ and 14% of invasive ductal carcinoma. The presence of this oncogene at high copy number may be a useful independent marker of poor prognosis and may be associated with **drug resistance** and correlated with tumor recurrence and shorter survival. EGFR could be measured in most breast tumors, and the level of its expression has inversely correlated with estrogen receptor protein expression. The value of EGFR as a predictor of prognosis remains controversial and is still being investigated. Cathepsin-D provides a provocative biologic rationale but is hindered by different and incongruent methods of analysis. The majority of large studies with more than 3-years' follow-up suggests that high cathepsin-D levels may be predictive of greater recurrence and lower survival. Angiogenesis has been implicated as a critical component of the metastatic process. Early studies show that tumor angiogenesis is an independent and highly significant prognostic indicator, and its presence may suggest the selection of "anti-angiogenic therapy."(ABSTRACT TRUNCATED AT 400 WORDS)

4/3,AB/23 (Item 23 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

08136221 94268820 PMID: 7911565
Antibody to **HER-2/neu** receptor blocks DNA repair after cisplatin in human breast and ovarian cancer cells.
Pietras R J; Fendly B M; Chazin V R; Pegram M D; Howell S B; Slamon D J
Division of Hematology-Oncology, University of California, Los Angeles 90024.
Oncogene (ENGLAND) Jul **1994**, 9 (7) p1829-38, ISSN 0950-9232 Journal Code: 8711562
Contract/Grant No.: CA01714-01; CA; NCI
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
Approximately 30% of human breast and ovarian cancers have amplification and/or overexpression of **HER-2/neu** gene which encodes a cell surface growth-factor receptor. Overexpression of this receptor, p185HER-2/**neu** , is associated with poor outcome and may predict clinical response to chemotherapy. Antibodies to **HER-2/neu** receptor have a cytostatic effect in suppressing growth of cells with overexpression of p185HER-2/**neu**. To elicit a cytocidal effect, therapy with antireceptor antibody was used in combination with the DNA-damaging **drug**, cisplatin, and this combined treatment produced a synergistic decrease in cell growth. In addition, antibody mediated an increased sensitivity to cisplatin in **drug-resistant** ovarian carcinoma cells containing multiple copies of **HER-2/neu** gene. To evaluate the mechanism for this synergy, unscheduled DNA synthesis was measured in cancer cells using incorporation of [3H]thymidine and autoradiography, and formation and repair of cisplatin-induced DNA adducts was also measured. Treatment with cisplatin led to a marked, dose-dependent increase in unscheduled DNA synthesis which was significantly reduced by combined treatment with antireceptor antibody in **HER-2/neu**-overexpressing cells. Therapy with antibody to **HER-2/neu** receptor also led to a 35-40% reduction in repair of cisplatin-DNA adducts after cisplatin exposure and, as a result, promoted **drug** -induced killing in target cells. This phenomenon which we term receptor-enhanced chemosensitivity may provide a rationale for more selective targeting and exploitation of overexpressed growth factor receptors in cancer cells, thus leading to new strategies for clinical

intervention.

4/3,AB/24 (Item 24 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

08115257 94238702 PMID: 7910218
P-glycoprotein and tumor progression.
Benchimol S; Ling V
Journal of the National Cancer Institute (UNITED STATES) Jun 1 **1994**, 86 (11) p814-6, ISSN 0027-8874 Journal Code: 7503089
Comment on J Natl Cancer Inst. 1994 Jun 1;86(11) 850-5; Comment on PMID 7910219
Document type: Comment; Editorial
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed

4/3,AB/25 (Item 25 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

08107971 94259184 PMID: 7911089
pp60v-src kinase overexpression leads to cellular **resistance** to the antiproliferative effects of tumor necrosis factor.
Aggarwal B B; Totpal K; Ali-Osman F; Budde R J; Pocsik E
Department of Clinical Immunology and Biological Therapy, University of Texas, M.D. Anderson Cancer Center, Houston 77030.
FEBS letters (NETHERLANDS) May 30 **1994**, 345 (2-3) p219-24, ISSN 0014-5793 Journal Code: 0155157
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
While some tumor cells are sensitive to the antiproliferative effects of tumor necrosis factor (TNF), others are **resistant**. The molecular basis for cellular **resistance** to TNF is not completely understood. Previously we have shown that transfection of cells with an oncogene HER2/**neu**/erb B2, a receptor tyrosine kinase, leads to **resistance** to the anticellular effects of TNF [(1988) Proc. Natl. Acad. Sci. USA 85, 5102-5106]. In the present study, we demonstrate that the overexpression of another oncogenic tyrosine kinase, pp60v-src also induces **resistance** to TNF. In contrast to HER2, however, pp60v-src transfection of cells did not lead to down-modulation of TNF receptors but rather to decreased intracellular glutathione levels. The pp60v-src-induced cellular **resistance** to TNF could be abrogated by interferon-gamma. Thus, these results indicate that the **resistance** of certain tumors to TNF may also be due in part to the overexpression of pp60v-src oncogene.

4/3,AB/26 (Item 26 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

08096855 94219837 PMID: 8166465
The molecular and cellular basis of human lung cancer.
Gazdar A F
Simmons Cancer Center, University of Texas Southwestern Medical Center, Dallas 75235-8590.
Anticancer research (GREECE) Jan-Feb **1994**, 14 (1B) p261-7, ISSN 0250-7005 Journal Code: 8102988
Document type: Journal Article; Review; Review, Tutorial
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed

Lung cancer arises after a series of morphological changes, which take several years to progress from normal epithelium to invasive cancer. The morphological changes progress from hyperplasia, to metaplasia, to dysplasia, to carcinoma in situ, to invasive cancer and finally to metastatic cancer. Multiple molecular changes have been documented in lung cancers, both small cell (SCLC) and non-small cell (NSCLC) types. The number of changes has been estimated to be in double digits. How can so many changes develop in one cell? One possible explanation is the "field cancerization" theory, that states that all or much of the aerodigestive tract epithelium has been mutagenized, perhaps as the result of exposure to tobacco products or other carcinogens. The molecular changes include activation of dominant oncogenes (myc family, K-ras and **HER/2/neu** genes), as well as loss of recessive growth regulatory genes or anti-oncogenes (p53, and rb as well as unidentified gene or genes on chromosome 3). However, cytogenetic and molecular genetic studies indicate that multiple other specific sites of actual or potential DNA loss may be present in lung cancers. Many of the well characterized molecular changes may function as negative prognostic factors for survival in subsets of lung cancers. Other changes may include development of **drug resistance** , and production of growth factors and their receptors. It is tempting to associate specific molecular changes with specific morphological changes, as has been attempted in the colon. However, because of the difficulties in serially sampling the respiratory tract, only a modest amount of data has been collected to date. It appears that deletions of chromosome 3p, hyperproliferation and aneuploidy are early changes, while p53 mutations appear later in the preneoplastic cascade. Documentation of intermediate markers for lung cancer and prospective studies of their prognostic effects will be necessary for the design of rational chemoprevention trials.

4/3,AB/27 (Item 27 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

08089298 94221534 PMID: 7909490

Prognostic significance of **HER-2/neu** oncoprotein expression in node-positive breast cancer. The influence of the pattern of immunostaining and adjuvant therapy.

Tetu B; Brisson J
Department of Pathology, Universite Laval, L'Hotel-Dieu de Quebec, Canada.

Cancer (UNITED STATES) May 1 **1994**, 73 (9) p2359-65, ISSN 0008-543X Journal Code: 0374236
Document type: Journal Article; Multicenter Study
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed

BACKGROUND. The influence of **HER-2/neu** on prognosis of breast cancer is controversial. The authors investigated by immunohistochemistry in node-positive disease the influence of the pattern of immunostaining (membranous or cytoplasmic) on outcome and the prognostic significance of this marker in patients receiving or not receiving adjuvant therapy. METHODS. The immunostaining for **HER-2/neu** oncoprotein was performed on formaldehyde-solution-fixed, paraffin-embedded sections of 888 node-positive breast cancers resected between 1980 and 1986 and for which a follow-up of 2.5-10.5 years was available. The staining was performed using a polyclonal antibody (dilution, 1/15). RESULTS. One hundred forty-three cases (16.1%) revealed a positive membrane staining with or without additional cytoplasmic contribution, whereas cytoplasmic staining alone was noted in 118 cases (13.3%). Positive membrane staining was correlated with more involved lymph nodes ($P = 0.005$), aneuploidy ($P = 0.002$), poor nuclear ($P < 0.0001$) and histologic ($P = 0.007$) grades, absence of estrogen ($P < 0.0001$) and progesterone ($P < 0.0001$) receptor content, and cathepsin D expression ($P = 0.009$). No relation was found ($P >$

0.05) with either age, tumor size, or HSP27 expression. Membrane staining was strongly associated with poor distant metastasis-free or overall survival rate (P < 0.0001), whereas cytoplasmic staining had no prognostic significance. Two hundred thirty-two patients (26.1%) received no additional treatment after surgery. The difference in survival rates between cases with positive and negative staining was only significant among patients submitted to adjuvant chemotherapy or hormone therapy. CONCLUSIONS. This study strongly supports the association of **HER-2/neu** oncoprotein expression with poor prognosis in node-positive breast cancer and demonstrates that membranous but not cytoplasmic staining is prognostically relevant. It also shows that **HER-2/neu** oncoprotein expression is useful in predicting survival time only in patients receiving adjuvant therapy, thus suggesting that it may be a marker of **drug resistance**.

4/3,AB/28 (Item 28 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

07820617 93352634 PMID: 7688739
Downstream signal transduction defects that suppress transformation in two revertant cell lines expressing activated rat **neu** oncogene.
Reardon D B; Hung M C
Department of Tumor Biology, University of Texas M.D. Anderson Cancer Center, Houston.
Journal of biological chemistry (UNITED STATES) Aug 25 **1993**, 268 (24) p18136-42, ISSN 0021-9258 Journal Code: 2985121R
Contract/Grant No.: 58880; PHS
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed

The **neu** gene encodes the transmembrane tyrosine kinase growth factor receptor, p185. To study **neu**-induced cellular transformation, we developed revertant cells from the **neu**-transformed NIH 3T3 cell line, B104-1-1, by treating the cells with the chemical mutagen ethyl methanesulfonate. The morphologically normal revertant cells were first selected by their ability either to attach to culture plates or to survive in the presence of the cytotoxic reagents colchicine or 5-fluoro-2-deoxyuridine. Two of the 21 candidate revertant cell lines isolated were further characterized and were found to lose their anchorage independence and ability to grow in 1% calf serum, indicating that they were nontransformed even though they still expressed p185 oncoprotein. The tyrosine residues of p185 in these two revertants were underphosphorylated, which may have contributed to their nontransformed status. In addition, these revertants also **resisted** transformation by **neu** and several additional oncogenes (H-ras, N-ras, v-mos, v-abl, and v-fos) as determined by focus forming assays. These results indicated that we had successfully developed, from **neu** -transformed cells, revertants exhibiting defective tyrosine phosphorylation of the **neu** oncoprotein. The results also suggested that **neu** and several other oncogenes may share common elements in their pathways for the induction of cellular transformation.

4/3,AB/29 (Item 29 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

07773704 93297863 PMID: 8100127
P-glycoprotein associated expression of c-fos and c-jun products in human lung carcinomas.
Volm M
German Cancer Research Center, Heidelberg.
Anticancer research (GREECE) Mar-Apr **1993**, 13 (2) p375-8,

ISSN 0250-7005 Journal Code: 8102988
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed

Surgical specimens of non-small cell lung carcinomas of 167 previously untreated patients were analyzed for expression of c-fos, c-jun, c-myc and c-**neu** products and for **resistance** to drugs. Because most of the patients were treated only by surgery, an in vitro test was used to determine the **resistance**. For the detection of the oncoproteins the streptavidin-biotin-peroxidase-complex method was used. An association between the **resistance** and c-fos and c-jun proteins was found (c-fos $p = 0.01$, c-jun $p = 0.09$), whereas a correlation between **resistance** and expression of c-**neu** and c-myc products was not observed. P-glycoprotein 170 was detected immunohistochemically in 91 tumors using the monoclonal antibody JSB-1. There was a significant correlation between the **resistance** measured by the in vitro test and P-glycoprotein 170 expression ($p < 0.001$). Also a significant correlation between the c-fos and c-jun proteins and the expression of P-glycoprotein was found (c-fos $p = 0.017$, c-jun $p = 0.036$). In contrast, no significant relationship was found between the expression of the c-**neu** or c-myc products and the expression of P-glycoprotein 170. Thus, there exists a significant relationship between **resistance**, P-glycoprotein 170, and c-fos and c-jun products in human non-small cell lung carcinomas. P-glycoprotein 170 may be regulated by the c-fos/c-jun protein complex, which binds specifically to AP-1.

4/3,AB/30 (Item 30 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

07771377 93310883 PMID: 1306309

The molecular biology of lung cancer.

Gazdar A F
Simmons Cancer Center, University of Texas Southwestern Medical Center, Dallas.

Tohoku journal of experimental medicine (JAPAN) Oct **1992**, 168 (2) p239-45, ISSN 0040-8727 Journal Code: 0417355
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed

Lung cancer arises after a series of morphological changes, which take several years to progress from normal epithelium to invasive cancer. The morphological changes progress from hyperplasia, to metaplasia, to dysplasia, to carcinoma in situ, to invasive cancer and finally to metastatic cancer. Multiple molecular changes have been documented in lung cancers, both small cell (SCLC) and non-small cell (NSCLC) types. The number of changes has been estimated to be in double digits. These changes include activation of dominant oncogenes myc family, (K-ras and **neu** genes), as well as loss of recessive growth regulatory genes or anti-oncogenes (p53, and RB as well as unidentified gene or genes on chromosome 3). However, cytogenetic and molecular genetic studies indicate that multiple other specific sites of actual or potential DNA loss may be present in lung cancers. Other changes may include development of **drug resistance**, and production of growth factors and their receptors. It is tempting to associate specific molecular changes with specific morphological changes, as has been attempted in the colon. However, because of the difficulties in serially sampling the respiratory tract, such studies have not been performed to date. Documentation of molecular changes in premalignant lesions and prospective studies of their prognostic effects will be necessary for the design of rational chemoprevention trials.

4/3,AB/31 (Item 31 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

07758501 93284516 PMID: 8099529
Expression of **resistance** factors (P-glycoprotein, glutathione S-transferase-pi, and topoisomerase II) and their interrelationship to proto-oncogene products in renal cell carcinomas.
Volm M; Kastel M; Mattern J; Efferth T
German Cancer Research Center, Heidelberg.
Cancer (UNITED STATES) Jun 15 **1993**, 71 (12) p3981-7, ISSN 0008-543X Journal Code: 0374236
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
BACKGROUND. This study investigates whether or not an interrelationship exists between the expression of **resistance** -related proteins (P-glycoprotein, glutathione S-transferase, topoisomerase II) and proto-oncogene products (c-fos, c-myc, c-K-ras, epidermal growth factor receptor [EGF-R], and c-**neu** proteins.) METHODS. Thirty-eight human renal cell carcinomas of previously untreated patients were analyzed for expression of P-glycoprotein (P-170), glutathione S-transferase-pi (GST-pi), topoisomerase II (Topo II) and proto-oncogene proteins by means of immunohistochemistry. Because of significant heterogeneity in most tumor biopsies, all analyses were done on tumor-derived primary cell culture lines on the third or fourth passage. RESULTS. An interrelationship between increased expression of P-170 and GST-pi and down-regulation of Topo II was found. Expression of the c-fos protein was seen in 66% of the tumors; expression of the c-myc protein, in 50%; of the c-K-ras protein, in 16%; of the EGF-R protein, in 61%; and of the c-**neu** protein, in 54% of the tumors. A significant correlation between the **resistance** factors and the c-fos, EGF-R, and c **neu**-proteins was observed (GST/c-fos, P = 0.012; Topo II/c-fos, P = 0.024; P-170/EGF-R, P < 0.001; GST/EGF-R, P = 0.018; Topo II/EGF-R, P = 0.027; P-170/c-**neu**, P = 0.005; GST/c-**neu**, P = 0.018; Topo II/EGF-R, P = 0.027; P-170/c-**neu**, P = 0.005; GST/c-**neu**, P = 0.008; Topo II/c-**neu**, P = 0.05). In contrast, interrelationships between **resistance** proteins and c-myc and c-K-ras proteins were not found. A significant interrelationship between the investigated **resistance** -related proteins or proto-oncogene proteins and the stage or grading of the tumors was not observed. CONCLUSIONS. The results demonstrate that in renal cell carcinomas a significant relationship exists between **resistance** -related proteins, such as P-170, GST-pi, or Topo II, and proto-oncogenes, such as c-fos, c-erbB1, and c-**neu**.

4/3,AB/32 (Item 32 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

07734415 93260725 PMID: 8098377
Correlation of intrinsic chemoresistance of non-small-cell lung cancer cell lines with **HER-2/neu** gene expression but not with ras gene mutations.
Tsai C M; Chang K T; Perng R P; Mitsudomi T; Chen M H; Kadoyama C; Gazdar A F
Chest Department, Veterans General Hospital-Taipei, Taiwan.
Journal of the National Cancer Institute (UNITED STATES) Jun 2 **1993**, 85 (11) p897-901, ISSN 0027-8874 Journal Code: 7503089
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
BACKGROUND: At diagnosis, most small-cell lung cancers (SCLCs) are

chemosensitive, whereas non-small-cell lung cancers (NSCLCs) are usually chemoresistant. Activation of ras genes and **HER-2/neu** genes (also known as ERBB2) is encountered in subpopulations of NSCLC but not in SCLC and has been linked to shortened survival. Therefore, activation of these genes may be associated with intrinsic chemoresistance in NSCLC. Studies have also suggested that the multidrug-**resistant** phenotype expressed by the MDR1 gene (also known as PGY1) does not correlate with the in vitro chemosensitivity of NSCLC cells or with clinical response to therapy and does not explain the spectrum of cross-**resistance** to drugs. PURPOSE: The purpose of this study was to investigate the relationships between chemoresistance and the presence of ras gene point mutations and overexpression of the **HER-2/neu** gene in NSCLC cell lines, which indicates gene activation. METHODS: Using a panel of 20 NSCLC cell lines established from untreated patients, we assessed the differences in **HER-2/neu** messenger RNA (mRNA) expression in the cell lines with or without ras mutations. We performed in vitro **drug** sensitivity testing by the tetrazolium-based MTT [i.e., 3-(4,5-dimethyl-2-thiazolyl)-2,5-diphenyl-2H-tetrazolium bromide] assay with doxorubicin, carmustine, cisplatin, melphalan, mitomycin, and etoposide, and we determined the differences in IC50 values (i.e., the **drug** concentrations required to inhibit cell growth by 50%) for the cell lines. RESULTS: We found a statistically significant correlation between the IC50 values for all six drugs and the degree of **HER-2/neu** gene expression in all 20 cell lines ($r = .67-.86$; $P < .005$) as well as in the subpopulation of eight cell lines with ras mutations ($r = .83-.98$; $P < .05$). The IC50 values for doxorubicin, carmustine, cisplatin, and melphalan were not significantly different in the cell lines with or without ras mutations, but the values for mitomycin and etoposide in lines with ras mutations were slightly lower than in those without ras mutations (borderline significance, $P = .031$). Levels of **HER-2/neu** expression in cell lines with ras mutations were lower than those without ras mutations, but the difference was not statistically significant. CONCLUSION: Our findings indicate that overexpression of **HER-2/neu** is a marker for intrinsic multidrug **resistance** in NSCLC cell lines. IMPLICATIONS: If the clinical relevance of our findings is confirmed, **HER-2/neu** gene expression can be used as a predictor of therapeutic failure in NSCLCs. The relationships between **HER-2/neu** gene expression, cell proliferation, and chemoresistance in NSCLC require further investigation.

4/3,AB/33 (Item 33 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

07663361 93184347 PMID: 8095168

Estrogen-dependent, tamoxifen-**resistant** tumorigenic growth of MCF-7 cells transfected with HER2/**neu**.

Benz C C; Scott G K; Sarup J C; Johnson R M; Tripathy D; Coronado E; Shepard H M; Osborne C K

Cancer Research Institute, University of California, San Francisco 94143.

Breast cancer research and treatment (NETHERLANDS) **1993**, 24 (2) p85-95, ISSN 0167-6806 Journal Code: 8111104

Contract/Grant No.: CA-30251; CA; NCI; CA-36773; CA; NCI; CA-44768; CA; NCI

Document type: Journal Article

Languages: ENGLISH

Main Citation Owner: NLM

Record type: Completed

Since the poor prognosis associated with HER2 amplified breast cancers might be explained by a mechanistic association between p185HER2 overexpression and therapeutic **resistance** , we assessed the chemo-endocrine sensitivity of estrogen receptor (ER) containing MCF-7 breast cancer cells transfected with full-length HER2 cDNA. Of the 36

isolated MCF/HER2 subclones, 7 were found to overexpress p185HER2 surface receptor at levels 3 to 45-fold greater than parental or control transfected cells (MCF/neo). The overexpressing transfectants possessed increased inositol-1,4,5-triphosphate-3'-kinase activity comparable to enzyme activity in the endogenously HER2 amplified breast cancer cell lines SK-Br-3 and BT-474. The anti-p185HER2 monoclonal antibody and receptor-specific partial agonist, muMAb4D5 (4D5), known to inhibit growth of SK-Br-3 and BT-474 cells, produced no significant growth inhibitory effect on any of the transfectants including the 45-fold overexpressing MCF/HER2-18 cells which were studied in greater detail. MCF/HER2-18 cells contained at least partially functioning exogenous receptor since 4D5 (3 micrograms/ml) specifically stimulated phosphorylation of p185HER2 and its co-precipitating ptyr56 substrate within 5 min, and this was followed at 1 h by a transient induction of c-myc but not c-fos mRNA. ER content and the in vitro sensitivity of MCF/HER2-18 cells to 5-fluorouracil and adriamycin were identical to those of control transfectants and parental cells. However, these highly overexpressing transfectants had acquired low level (2 to 4-fold) **resistance** to cisplatin and were no longer sensitive to the antiestrogen tamoxifen (TAM). To compare the hormone-dependent tumorigenicity of the HER2 transfectants, MCF/HER2-18 and control cells (MCF, MCF/neo-3) were implanted into ovariectomized athymic nude mice. No tumors were produced in the absence of estradiol (E2) administration. In E2 supplemented mice, MCF/HER2-18 tumors grew most rapidly. When E2 treatment was stopped and daily TAM injections were initiated, MCF-7 and MCF/neo-3 tumor growth ceased immediately, while MCF/HER2-18 tumors continued to show an accelerated growth rate lasting weeks. This pattern of hormone-dependent, TAM-**resistant** growth exhibited by the MCF/HER2-18 tumors in nude mice supports the possibility that p185HER2 overexpression in human breast cancers may be linked to therapeutic **resistance**.

4/3,AB/34 (Item 34 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

07533250 93057620 PMID: 1331337
Oncogenes: cause or consequence in the development of glial tumors.
Akbasak A; Sunar-Akbasak B
Clinical Neurosurgery Section, National Institute of Neurological Disorders and Stroke, Bethesda, MD 20892.
Journal of the neurological sciences (NETHERLANDS) Sep **1992**, 111 (2) p119-33, ISSN 0022-510X Journal Code: 0375403
Document type: Journal Article; Review; Review, Academic
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed

Recent developments in the field of oncogenes and growth stimulatory factors have provided limited but essential models in neuro-oncology. The observation in gliomas of platelet growth factor (PDGF)-like immunoreactivity fits with the autocrine secretion model, rising the possibility for the growth factor independence of the cancer cells. The discovery of the tumor suppressor genes, for which loss of function mutations are oncogenic as in the RB gene of the retinoblastoma and p53 gene, has introduced a new concept of oncogenesis which could be useful even in the cure of the neoplasms. Several oncogenes are amplified and/or expressed in brain tumors, some associated with polymorphism leading to abnormal protein products. Therefore, corresponding functions, such as production of deficient epidermal growth factor receptor (EGFR) encoded by erb-B, are impaired. Abnormal chromosomal patterns have been recognized in brain tumors and found mainly in chromosomes 7 and 22 on which oncogenes erb-B and sis are located, respectively. Location of proto-oncogenes, which are normally expressed in the brain, indicate that they share common distribution patterns mainly involving the cerebellum, hippocampus and olfactory bulbs. These proto-oncogenes may be regulated by physiological and pathological events. The concept of oncogene involvement in brain

tumors must be extended to include the other factors such as G-proteins, growth factor receptors, membrane-associated and cytoplasmic protein kinases, which are all responsible for the control of the cell growth and their response to external signals including chemotherapeutic drigs.

4/3,AB/35 (Item 35 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

07528036 93054951 PMID: 1429859
Platelet endothelial cell adhesion molecule, PECAM-1, modulates cell migration.
Schimmenti L A; Yan H C; Madri J A; Albelda S M
Department of Pathology, Yale University School of Medicine, New Haven, Connecticut 06510.
Journal of cellular physiology (UNITED STATES) Nov **1992**, 153 (2) p417-28, ISSN 0021-9541 Journal Code: 0050222
Contract/Grant No.: 726-U-41-54759; PHS; IF32 HL08546-01; HL; NHLBI; RO1-HL28373; HL; NHLBI; +
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed

Cell migration is an important process in such phenomena as growth, development, and wound healing. The control of cell migration is orchestrated in part by cell surface adhesion molecules. These molecules fall into two major categories: those that bind to extracellular matrix and those that bind to adjacent cells. Here, we report on the role of a cell-cell adhesion molecule, platelet-endothelial cell adhesion molecule-1, (PECAM-1), a member of the lg superfamily, in the modulation of cell migration and cell-cell adhesion. PECAM-1 is a 120-130 kDa integral membrane protein that resides on endothelial cells and localizes at sites of cell-cell contact. Since endothelial cells express PECAM-1 constitutively, we studied the effects of PECAM-1 on cell-cell adhesion and migration in a null-cell population. Specifically, we transfected NIH/3T3 cells with the full length PECAM-1 molecule (two independent clones). Transfected cells containing only the neomycin **resistance** gene, cells expressing a construct coding for the extracellular domain of the molecule, and cells expressing the **neu** oncogene were used as controls. The PECAM-1 transfectants appeared smaller and more polygonal and tended to grow in clusters. Indirect immunofluorescence of PECAM-1 transfectants showed peripheral staining at sites of cell-cell contact, while the extracellular domain transfectants and the control cells did not. In two quantitative migration assays, the full-length PECAM-1 transfectants migrated more slowly than control cells. Thus, PECAM-1 transfected into a null cell appears to localize to sites of cell-cell contact, promote cell-cell adhesion, and diminish the rate of migration. These findings suggest a role for this cell-cell adhesion molecule in the process of endothelial cell migration.

4/3,AB/36 (Item 36 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

07519543 93045610 PMID: 1358410
Clinical significance of erbB-2 (**HER-2/neu**) protein.
Paik S
Vincent T. Lombardi Cancer Center, Georgetown University Medical Center, Washington, D.C.
Cancer investigation (UNITED STATES) **1992**, 10 (6) p575-9, ISSN 0735-7907 Journal Code: 8307154
Document type: Journal Article; Review; Review, Tutorial
Languages: ENGLISH
Main Citation Owner: NLM

Record type: Completed
erbB-2 protein is believed to be a cell membrane receptor for the recently identified ligand gp30. When overexpressed, erbB-2 is an indicator of poor prognosis in adenocarcinomas of breast, stomach, lung, and endometrium. Even more important, clinical data suggest that erbB-2 overexpression may be an indicator of poor response to at least some commonly used adjuvant regimens. However, there is preliminary evidence that these tumors might respond as well to doxorubicin regimen as do erbB-2 negative tumors, at least in gastric cancer. The efficacy of doxorubicin-containing regimen in the treatment of tumors with erbB-2 overexpression needs to be explored further by retrospective analysis of finished clinical trials. Combination of chemotherapeutics with reagents that block erbB-2 signal transduction pathway may be another effective approach.

4/3,AB/37 (Item 37 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

07502410 93026378 PMID: 1328988
Azatyrosine inhibits neurite outgrowth of PC12 cells induced by oncogenic Ras.
Fujita-Yoshigaki J; Yokoyama S; Shindo-Okada N; Nishimura S
Department of Biophysics and Biochemistry, Faculty of Science, University of Tokyo, Japan.
Oncogene (ENGLAND) Oct **1992**, 7 (10) p2019-24, ISSN 0950-9232
Journal Code: 8711562
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
An antibiotic, azatyrosine [L-beta-(5-hydroxy-2-pyridyl) alanine], specifically converts ras-, raf- or c-erbB2 (**neu**)-transformed NIH3T3 cells to apparently normal phenotype. The reversion induced by azatyrosine is permanent, and the phenotype of the revertant cells does not change even after prolonged culture in the absence of azatyrosine [N. Shindo-Okada, O. Manabe, H. Nagahara & S. Nishimura (1989). Mol. Carcinogen., 2, 159-167]. In the present study, we found that neurite outgrowth of PC12 cells induced by expression of either the ras or raf oncogenes was inhibited by addition of azatyrosine to the medium. Azatyrosine also inhibited neurite outgrowth induced by microinjection of oncogenic Ras protein into PC12 cells. The dose dependency was much the same for the two systems, inhibition of neurite outgrowth of PC12 cells and reversion of the transformed NIH3T3 cells. Microinjection of azatyrosine into the cells was as effective as addition to the medium, indicating that the target of azatyrosine is intracellular. In contrast, neurite outgrowth induced by nerve growth factor, which has been shown to be mediated by normal Ras [N. Hagag, S. Halegouna & M. Viola (1986). Nature, 319, 680-682], was found to be **resistant** to azatyrosine. Azatyrosine also showed no effect on neurite outgrowth induced by a membrane-permeant cyclic AMP analog through another pathway. These findings suggest that azatyrosine sensitivity is the result of abnormal signal transduction by oncogenic Ras. It was shown that azatyrosine also inhibited differentiation-associated growth arrest of PC12 cells induced by oncogenic Ras. In Ras-induced neurite outgrowth, the azatyrosine-sensitive process was found to be completed in the first 6-9 h, and is probably essential for the commitment of PC12 cells to differentiation rather than to growth.

4/3,AB/38 (Item 38 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

07383580 92314458 PMID: 1319775
Selective formation of tumor necrosis factor-alpha (TNF) degradation

products contributes to TNF mediated cytotoxicity.
Fruehauf J P; Sinha B K
Section of Biochemical and Molecular Pharmacology, National Cancer Institute, National Institutes of Health, Bethesda, Maryland.
Oncology research (UNITED STATES) **1992**, 4 (3) p91-101, ISSN 0965-0407 Journal Code: 9208097
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
We compared tumor necrosis factor (TNF) metabolism by wild-type MCF-7 (WT) cells, by 40-fold doxorubicin **resistant** (40F) breast cancer cells and by PC3 and LNCaP prostate cancer cell lines. MCF-7 WT and LNCaP cell lines were sensitive to TNF cytotoxicity and both lines produced two major intracellular TNF degradation products of 15 kDa and 5.5 kDa. The MCF-7 40F and the PC3 cell lines were **resistant** to TNF and produced multiple TNF degradation products with molecular weights lower than 15 kDa. Both the breast and prostate lines showed TNF receptor crosslinking patterns consistent with a molecular weight of 55 kDa. The breast and LNCaP lines expressed TNF receptors with an apparent dissociation constant (Kd) of 0.4 to 0.6 nM, while the TNF **resistant** line had a Kd of 2 nM. Similar receptor numbers per cell were found for all cell types (4,000 to 8,000/cell), and comparable levels of TNF internalization were noted. TNF-conditioned medium from the TNF-sensitive cell types was cytotoxic toward both the TNF-sensitive and TNF-**resistant** lines, and the toxicity was significantly blocked by an anti-TNF monoclonal antibody. Hydrophobic interaction column HPLC fractionation of the TNF-degradation products produced by MCF-7 WT and LNCaP cells revealed that the trimeric, monomeric, and 5.5 kDa fractions possessed the greatest in vitro antitumor activity. These findings suggest that a TNF degradation product, produced selectively by TNF-sensitive cells, may contribute to the antitumor action of TNF.

4/3,AB/39 (Item 39 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

07367529 92300405 PMID: 1351537
Prognostic significance of **HER-2** oncoprotein expression in breast cancer: a 30-year follow-up.
Toikkanen S; Helin H; Isola J; Joensuu H
Department of Pathology, University Central Hospital, Turku, Finland.
Journal of clinical oncology : official journal of the American Society of Clinical Oncology (UNITED STATES) Jul **1992**, 10 (7) p1044-8, ISSN 0732-183X Journal Code: 8309333
Comment in J Clin Oncol. 1992 Jul;10(7) 1034-6; Comment in PMID 1351536
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
PURPOSE: To study retrospectively the long-term prognostic significance of **HER-2** oncoprotein expression in breast cancer (BC). PATIENTS AND METHODS: Two hundred nine consecutive female patients with invasive operable BC from a defined urban population were observed for a median of 30 years. Tissue expression of **HER-2** oncoprotein was demonstrated by using an immunoperoxidase procedure. RESULTS: Fifty-five (26%) patients had cancer and a positive **HER-2** oncoprotein stain reaction. They had significantly worse 10- and 25-year survival rates than those patients who had a negative stain reaction in their cancer (31% v 48% and 31% v 39%, respectively; P = .004). **HER-2** expression was also associated with a poorer survival among patients who had axillary nodal metastases (P = .003; n = 104), but not among those patients who did not have metastases. **HER-2** expression was related to the ductal histologic type, poor histologic grade, and high mitotic count, but not to

tumor size, axillary nodal status, DNA ploidy, or S-phase fraction (SPF). In a multivariate analysis among patients with nodal metastases, **HER-2** expression was an independent prognostic factor (P = .04) that predicted poor survival. However, if the entire series was entered onto the analysis, it did not emerge as an independent factor. CONCLUSIONS: **HER-2** oncoprotein expression has long-term prognostic significance for predicting poor survival in BC, and it has an independent prognostic value among patients who presented with axillary nodal metastases. This result is contradictory to the argument that **HER-2** expression is only a marker for **drug resistance** because the patients were not given adjuvant **drug** therapy.

4/3,AB/40 (Item 40 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

07302677 92231503 PMID: 1348920
Oncoprotein (c-myc, c-erbB1, c-erbB2, c-fos) and suppressor gene product (p53) expression in squamous cell carcinomas of the lung. Clinical and biological correlations.
Volm M; Efferth T; Mattern J
German Cancer Research Center, Heidelberg.
Anticancer research (GREECE) Jan-Feb **1992**, 12 (1) p11-20,
ISSN 0250-7005 Journal Code: 8102988
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
The expression of the protooncogene encoded proteins (c-erbB1, c-erb B2, c-myc, c-fos) and the suppressor gene product p53 was analyzed in 81 human squamous cell carcinomas of the lung and correlated with clinical parameters of the patients (patient survival, presence of metastases and tumor stage) and with biological characteristics of the tumors (tumor growth in nude mice, DNA-ploidy, proliferative activity, **drug-resistance** and P-glycoprotein or gluathione S-transferase expression). By means of immunohistochemistry, expression of c-erbB1 oncoprotein (EGF-receptor) was detected in 79% of the tumors, c-erbB2 (c-**neu**) proteins in 35%, c-myc proteins in 48%, c-fos proteins in 41%, and p53 in 43% of the tumors. Patients with c-erbB1 positive tumors had a poor prognosis (p = 0.021). In addition, these tumors were more frequently **drug resistant** (p = 0.0067). A significant correlation between the growth of the squamous lung carcinomas in nude mice and c-fos oncoprotein expression was demonstrated (p = 0.017). Therefore, EGF-receptor and c-fos products may serve as prognostic factors for the aggressiveness of squamous cell carcinomas of the lung and for the response of these tumors to chemotherapy. No significant correlation was found between the expression of the c-erbB1 or c-fos gene products and stage, metastasis and DNA-ploidy. In contrast to these results, no relationship was found between c-**neu** or c-myc gene products expression and any of the clinical or biological parameters examined. Aneuploid squamous cell carcinomas of the lung expressed p53 more frequently than diploid tumors (p = 0.027). However, there was no significant difference between p53 expression and stage, survival of patients, metastasis, growth of the tumors in nude mice, proliferative activity and **drug-resistance** of the tumors.

4/3,AB/41 (Item 41 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

07279216 92208966 PMID: 1348216
Effects of beta-2 microglobulin anti-sense oligonucleotides on sensitivity of HER2/**neu** oncogene-expressing and nonexpressing target cells to lymphocyte-mediated lysis.

Lichtenstein A; Fady C; Gera J F; Gardner A; Chazin V R; Kelley D; Berenson J
Department of Medicine, V.A. Wadsworth UCLA Medical Center.
Cellular immunology (UNITED STATES) Apr 15 **1992**, 141 (1) p219-32, ISSN 0008-8749 Journal Code: 1246405
Contract/Grant No.: CA-16042; CA; NCI
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
The mechanism by which HER2/**neu** overexpressing tumor cells **resist** NK, LAK, and LDCC cytotoxic lymphocytes was investigated. **Resistance** was not explained by a delay in kinetics of lysis, concurrent **resistance** to TNF, or a diminished expression of the transferrin receptor. HLA-class I expression, however, was markedly elevated compared to HER2 nonexpressing targets suggesting a reason for **resistance** . To test the role of class I, we selectively decreased expression by incubation of targets with beta-2 microglobulin anti-sense oligonucleotides. Anti-sense-treated HER2+ targets, displaying levels of class I comparable to HER2- targets, were still markedly **resistant** to cytotoxic effectors. Down-regulation of class I expression in HER2- carcinoma cells also had no effect on sensitivity to cytotoxicity by anti-sense treatment of Raji and U937 targets resulted in enhanced sensitivity to NK and LAK effectors but not to T cells mediating LDCC. These data indicate **resistance** to cytotoxicity in HER2-expressing targets cannot be solely explained by heightened expression of class I. The data also support the concept that class I expression regulates sensitivity to NK and LAK cells (but not LDCC effectors) in selected targets.

4/3,AB/42 (Item 42 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

07243901 92181812 PMID: 1686710
New mechanisms of gene amplification in **drug resistance** (the episome model).
Von Hoff D D
Cancer treatment and research (NETHERLANDS) **1991**, 57 p1-11, ISSN 0927-3042 Journal Code: 8008541
Document type: Journal Article; Review; Review, Tutorial
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed

4/3,AB/43 (Item 43 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

07222054 92145613 PMID: 1346583
Interferon-induced increase in sensitivity of ovarian cancer targets to lysis by lymphokine-activated killer cells: selective effects on HER2/**neu**-overexpressing cells.
Fady C; Gardner A M; Gera J F; Lichtenstein A
Department of Medicine, V.A. Wadsworth-UCLA Medical Center.
Cancer research (UNITED STATES) Feb 15 **1992**, 52 (4) p764-9, ISSN 0008-5472 Journal Code: 2984705R
Contract/Grant No.: CA16042; CA; NCI
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
Overexpression of the HER2/**neu** oncogene in ovarian tumor cells is associated with relative **resistance** to lymphokine-activated killer (LAK) cell cytotoxicity. Treatment with gamma-interferon (IFN-gamma)

(200-2000 units/ml) for 3 days markedly enhanced the sensitivity of HER2/**neu**-overexpressing ovarian tumor cells to LAK cells but had no effect on the sensitivity of nonexpressing ovarian targets. Increased sensitivity to lysis was associated with an increase in effector-target conjugate formation, the induction of target cell intercellular adhesion molecule 1 (ICAM-1) expression, and the down-regulation of HER2/**neu** expression. Anti-ICAM-1 antibody blocked the enhanced lysis, indicating that ICAM-1 is important in the increased sensitivity to LAK cells. However, induction of ICAM-1 expression did not correlate well with enhanced sensitivity to lysis; it was maximal after 24 h of exposure to IFN-gamma and still present 24 h after removing IFN-gamma. In contrast, enhanced lysis required 3 days of exposure to IFN-gamma and was reversed within 24 h after removal of IFN-gamma. These data indicate that, although ICAM-1 is necessary, it is not sufficient for the IFN-gamma-induced enhancement of sensitivity to LAK lysis.

4/3,AB/44 (Item 44 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

07165497 92075359 PMID: 1835847
MDR1 gene expression and prognostic factors in primary breast carcinomas.
Wallner J; Depisch D; Hopfner M; Haider K; Spona J; Ludwig H; Pirker R
Clinic for Internal Medicine I, Vienna, Austria.
European journal of cancer (Oxford, England : 1990) (ENGLAND) **1991**, 27 (11) p1352-5, ISSN 0959-8049 Journal Code: 9005373
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
To prospectively assess the role of the MDR1 gene in breast carcinomas, MDR1 RNA levels of breast carcinoma specimens were determined by slot blot analysis. In 59 evaluable patients with primary breast carcinomas, MDR1 RNA levels of the carcinomas were negative in 54%, low in 29% and high in 17% of the patients. No differences in age, menopause status, oestrogen and progesterone receptor levels, tumour size, lymph node involvement and c-erbB-2/**neu** gene expression were observed between MDR1 RNA negative patients and MDR1 RNA positive patients.

4/3,AB/45 (Item 45 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

07154972 92089224 PMID: 1684294
Molecular biology of ovarian cancer.
Kacinski B M; Chambers S K
Yale University School of Medicine, New Haven, Connecticut.
Current opinion in oncology (UNITED STATES) Oct **1991**, 3 (5) p889-900, ISSN 1040-8746 Journal Code: 9007265
Document type: Journal Article; Review; Review, Tutorial
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
This minireview, which due to the limitations of space cannot claim to be exhaustive, summarizes major advances in molecular biologic research on ovarian surface epithelial (adeno)carcinomas communicated approximately between the beginning of April 1990 through the end of March 1991. We focus primarily on studies of oncogenes, peptide hormone growth factors and their receptors, steroid hormone receptors, cytogenetics and flow cytometry, and **resistance** to therapy with cytotoxic agents.

4/3,AB/46 (Item 46 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

07070810 92005459 PMID: 1680547
Requirements for the internalization of a murine monoclonal antibody directed against the **HER-2/neu** gene product c-erbB-2.
Maier L A; Xu F J; Hester S; Boyer C M; McKenzie S; Bruskin A M; Argon Y; Bast R C
Department of Medicine, Duke Comprehensive Cancer Center, Duke University Medical Center, Durham, North Carolina 27710.
Cancer research (UNITED STATES) Oct 1 **1991**, 51 (19) p5361-9, ISSN 0008-5472 Journal Code: 2984705R
Contract/Grant No.: 5-R01-CA 39930; CA; NCI
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
A murine monoclonal antibody, TA1, is directed against an epitope on the extracellular domain of the **HER-2/neu** (c-erbB-2) gene product. Requirements for TA1-induced internalization of c-erbB-2 have been studied using the SKBr3 human breast cancer cell line and several rat fibroblast cell lines that express either wild-type or mutant human c-erbB-2. Internalization of TA1 was monitored by assaying protease-**resistant** uptake of 125I-labeled TA1, by electron microscopy of gold-labeled TA1, and by inhibition of clonogenic growth of cells incubated with TA1 that had been conjugated with blocked ricin. Similar rates of internalization of TA1 were observed in SKBr3 and in rat fibroblasts that expressed human c-erbB-2. The route of endocytosis was the same as that observed with antibodies against other membrane receptors. Anti-c-erbB-2 and anti-transferrin receptor cointernalized through clathrin-coated pits, coated vesicles, endosomes, and multivesicular bodies. Products of mutant c-erbB-2 that lacked a portion of the tyrosine kinase domain or that lacked most of the cytoplasmic domain were endocytosed in the presence of TA1 as promptly as the wild-type c-erbB-2 product. Slightly more rapid internalization of TA1 was observed in rat cells that expressed c-erbB-2 with a single point mutation in the transmembrane domain. Taken together, our data suggest that neither the intracytoplasmic domain nor receptor phosphorylation is required for antibody-mediated endocytosis of c-erbB-2.

4/3,AB/47 (Item 47 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

06918472 91228995 PMID: 2028918
Current status of adjuvant therapy of early breast cancer.
Ziegler L D; Buzdar A U
University of Texas M. D. Anderson Cancer Center, Houston.
American journal of clinical oncology : the official publication of the American Radium Society (UNITED STATES) Apr **1991**, 14 (2) p101-10 , ISSN 0277-3732 Journal Code: 8207754
Document type: Journal Article; Review; Review, Tutorial
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
Adjuvant therapy in operable breast cancer (stage I and II) can significantly reduce the risk of recurrences and improve survival. In stage I disease, 20-30% of patients will eventually recur. Several prognostic factors may help in identifying poor prognostic subgroups of stage I patients, including ER and PR status, flow cytometry data, nuclear grade, **neu** oncogene expression, and perhaps haptoglobin-related protein, Cathepsin-D, and Ki-67 expression. Single-agent chemotherapy and oophorectomy have not resulted in prolongation of survival. Combination chemotherapy regimens are superior to single agents, and doxorubicin-containing regimens may be superior to non-doxorubicin-containi ng regimens. Tamoxifen is effective in improving survival in patients who are ER positive, particularly those women older than 50 years. It appears

4/3,AB/59 (Item 4 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
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09829196 BIOSIS NO.: 199598284114
Selective cytotoxic effect of tamoxifen on epithelial and fibroblastic cells transformed by different oncogenes.
AUTHOR: Sanchez-Prieto R; Vargas J A; Durantez A; Anaya A; Ramon Y Cajal S (a)
AUTHOR ADDRESS: (a)Dep. Patologia, Clinica Puerta Hierro, c/San Martin Porres 4, 28035 Madrid**Spain
JOURNAL: Oncology Reports 2 (3):p457-459 **1995**
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: To study the correlation between oncogenes and the cytotoxic effect of tamoxifen in estrogen negative (ER) cells, we transformed mouse keratinocyte and fibroblastic cell lines with several oncogenes and studied cell viability, thymidine incorporation and PKC levels. We show that v-myc and v-H-ras oncogenes increase sensitivity in both cell types and that **Neu** and mutant p53 also increase sensitivity to tamoxifen, more significantly in the epithelial cells. Conversely, transformation with adenovirus E1a oncogene induces **resistance** to tamoxifen in both cell types. These results indicate that tamoxifen may be effective in different kinds of malignant cells depending on the oncogenic alterations present in the cells.

1995

4/3,AB/60 (Item 5 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
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09751711 BIOSIS NO.: 199598206629
Overexpression of c-**neu** confers multidrug **resistance** behavior on murine mammary epithelial cells.
AUTHOR: Taylor B E; Sheffield L G
AUTHOR ADDRESS: Endocrinol.-Reproductive Physiol., Univ. Wisconsin, Madison, WI 53706**USA
JOURNAL: FASEB Journal 9 (3):pA95 **1995**
CONFERENCE/MEETING: Experimental Biology 95, Part I Atlanta, Georgia, USA April 9-13, 1995
ISSN: 0892-6638
RECORD TYPE: Citation
LANGUAGE: English
1995

4/3,AB/61 (Item 6 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
(c) 2002 BIOSIS. All rts. reserv.

09292463 BIOSIS NO.: 199497300833
No correlation of **HER-2/neu** gene expression with acquired chemoresistance in non-small cell lung cancer cell lines.
AUTHOR: Chang K-T; Tsai C-M; Perng R-P; Chen M-H; Ku T-Y; Lai S-L
AUTHOR ADDRESS: Chest Dep., Veterans Gen. Hosp., Taipei 11217**Taiwan
JOURNAL: Proceedings of the American Association for Cancer Research Annual Meeting 35 (0):p9 **1994**
CONFERENCE/MEETING: 85th Annual Meeting of the American Association for Cancer Research San Francisco, California, USA April 10-13, 1994
ISSN: 0197-016X

RECORD TYPE: Citation
LANGUAGE: English
1994

4/3,AB/62 (Item 7 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
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08902503 BIOSIS NO.: 199396054004
Clinical evaluation of californium-252 neutron intracavitary therapy for primary endometrial adenocarcinoma.
AUTHOR: Maruyama Yosh(a); Van Nagell John R; Yoneda Justine; Depriest Paul; Kryscio Richard J
AUTHOR ADDRESS: (a)Radiation Oncol., Gershenson Oncol. Cent., Wayne State Univ., Detroit, MI 48201**USA
JOURNAL: Cancer (Philadelphia) 71 (12):p3932-3937 **1993**
ISSN: 0008-543X
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Background. A pilot feasibility study of the neutron-emitting radioisotope 252Cf was done on patients with uterine adenocarcinoma and medically inoperable disease or unfavorable G3 histologic findings. Methods. 252Cf intracavitary therapy was combined with 40-45 Gy of fractionated whole-pelvis photon therapy. In select patients, hysterectomy was performed. Results. Thirty-one patients with Stage I-III adenocarcinoma of the corpus uteri were treated with 252Cf neutron brachytherapy. The patients treated often were in poor general medical condition and had multiple chronic medical illnesses for which conventional radiation and surgery usually would not be recommended. 252Cf allowed short implant treatment time (hours), was usable in a small number of insertions (the average number of insertions was two), and was useful for treating large volume tumors. Stage and grade of the tumor were important determinants of patient survival. The 5-year actuarial survival was 83% for patients with Stage I disease but only 37% for those with Stage II disease (primarily adenosquamous cell carcinomas). The 5-year survival was 100% for patients with Grade 1 tumors, 88% for those with Grade 2 tumors, and 21% for those with Grade 3 tumors. Conclusion. 252Cf neutron brachytherapy was found to be an effective and well-tolerated therapy for endometrial carcinoma. The excellent therapeutic efficacy and good patient tolerance make it suitable for additional evaluation in future Phase II-III trials.

1993

4/3,AB/63 (Item 8 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
(c) 2002 BIOSIS. All rts. reserv.

08286401 BIOSIS NO.: 000043052474
HER2-**NEU** VARIANT TRANSCRIPT POTENTIALLY ASSOCIATED WITH **RESISTANCE** TO ANTI-HER2 THERAPY
AUTHOR: ROBLES R; SCOTT G K; PARK J W; SHEPARD H M; BENZ C C
AUTHOR ADDRESS: CANCER RES. INST., UNIV. CALIF., SAN FRANCISCO, CALIF. 94143, USA.
JOURNAL: 83RD ANNUAL MEETING OF THE AMERICAN ASSOCIATION FOR CANCER RESEARCH, SAN DIEGO, CALIFORNIA, USA, MAY 20-23, 1992. PROC AM ASSOC CANCER RES ANNU MEET 33 (0). 1992. 374. **1992**
CODEN: PAMRE
DOCUMENT TYPE: Meeting
RECORD TYPE: Citation

LANGUAGE: ENGLISH
1992

4/3,AB/64 (Item 9 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
(c) 2002 BIOSIS. All rts. reserv.

06565178 BIOSIS NO.: 000087007339
ANALYSIS OF GENE AMPLIFICATION IN HUMAN TUMOR CELL LINES
AUTHOR: FUKUMOTO M; SHEVRIN D H; RONINSON I B
AUTHOR ADDRESS: DEP. GENET., UNIV. ILL. COLL. MED., CHICAGO, ILL. 60612.
JOURNAL: PROC NATL ACAD SCI U S A 85 (18). 1988. 6846-6850. **1988**
FULL JOURNAL NAME: Proceedings of the National Academy of Sciences of the United States of America
CODEN: PNASA
RECORD TYPE: Abstract
LANGUAGE: ENGLISH

ABSTRACT: Oncogene amplification has been observed in various primary tumors and tumor-derived cell lines. In several types of cancer, amplification of specific oncogenes is correlated with the stage of tumor progression. To estimate the frequency of gene amplification in other tumor types and to determine whether the ability to grow in vivo is associated with gene amplification in tumor cell lines, we have developed a modified version of the in-gel renaturation assay that detects human DNA sequences of unknown nature amplified as little as 7- to 8-fold. This assay was used to screen 16 cell lines derived from various solid tumors and leukemias. Amplified DNA sequences were detected in only one cell line, Calu-3 lung adenocarcinoma. This cell line was found to contain coamplified NGL (formerly termed **neu**) and ERBA1 oncogenes. However, when one of the amplification-negative cell lines, PC-3 prostatic carcinoma, was selected for in vivo growth in nude mice, amplified DNA sequences became detectable in these cells. The amplified sequences included the MYC oncogene, which showed no amplification in the parental cell line but was amplified 10- to 12-fold in the in vivo-selected cells. MYC amplification may, therefore, provide tumor cells with a selective advantage specific for in vivo growth.

1988

4/3,AB/65 (Item 10 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
(c) 2002 BIOSIS. All rts. reserv.

05948017 BIOSIS NO.: 000035039380
LOSS OF TUMORIGENICITY OF MULTIDRUG **RESISTANT** NIH3T3 CELLS TRANSFORMED WITH C-ERB2-**NEU** ONCOGENE
AUTHOR: KUO M T; HUNG M; CHEN X-S
AUTHOR ADDRESS: DEP. MOL. PATHOL. TUMOR BIOL., UNIV. TEXAS M.D. ANDERSON HOSP., HOUSTON, TEX. 77030.
JOURNAL: 79TH ANNUAL MEETING OF THE AMERICAN ASSOCIATION FOR CANCER RESEARCH, NEW ORLEANS, LOUISIANA, USA, MAY 25-28, 1988. PROC AM ASSOC CANCER RES ANNU MEET 29 (0). 1988. 292. **1988**
CODEN: PAMRE
DOCUMENT TYPE: Meeting
RECORD TYPE: Citation
LANGUAGE: ENGLISH
1988

4/3,AB/66 (Item 11 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

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05875184 BIOSIS NO.: 000034098333
THE INTERACTIONS OF EXPRESSED ONCOGENES IN CARCINOMA OF THE BREAST
AUTHOR: YEE L; KACINSKI B; CARTER D; DONOFRIO L; ENG M
AUTHOR ADDRESS: YALE UNIV. SCH. MED., NEW HAVEN, CONN.
JOURNAL: 77TH ANNUAL MEETING OF THE USA AND CANADIAN ACADEMY OF PATHOLOGY (USA-CANADIAN DIVISION OF THE INTERNATIONAL ACADEMY OF PATHOLOGY), WASHINGTON, D.C., USA, FEBRUARY 28-MARCH 4, 1988. LAB INVEST 58 (1). 1988. 106A. **1988**
CODEN: LAINA
DOCUMENT TYPE: Meeting
RECORD TYPE: Citation
LANGUAGE: ENGLISH
1988

4/3,AB/67 (Item 12 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
(c) 2002 BIOSIS. All rts. reserv.

05538247 BIOSIS NO.: 000083011386
PENETRATION OF CEFMENOXIME INTO CEREBROSPINAL FLUID OF PATIENTS WITH BACTERIAL MENINGITIS
AUTHOR: HUMBERT G; VEYSSIER P; FOURTILLAN J-B; BRYSKIER A; BORSA F; LALLEMENT P Y; BONMARCHAND G
AUTHOR ADDRESS: DEP. INFECTIOUS DISEASES, CHARLES NICOLLE HOSPITAL, ROUEN 76031, FRANCE.
JOURNAL: J ANTIMICROB CHEMOTHER 18 (4). 1986. 503-506. **1986**
FULL JOURNAL NAME: Journal of Antimicrobial Chemotherapy
CODEN: JACHD
RECORD TYPE: Abstract
LANGUAGE: ENGLISH

ABSTRACT: Cefmenoxime is a new semisynthetic third generation cephalosporin particularly **resistant** to .beta.-lactamase activity and with a high degree of activity against a wide variety of pathogens, including those frequently causing bacterial meningitis (**Neu** & Labthavikul, 1982). The study reported here was undertaken to determine the extent of cefmenoxime penetration into the cerebrospinal fluid (CSF) of patients with bacterial meningitis.
1986

that six cycles of an effective regimen is as effective as more prolonged administration of the same drugs, and drugs should be given at the optimal dose rate. Preliminary results of alternating non-cross-**resistant** chemotherapy regimens show promise, but additional data are needed to determine its impact on survival.

4/3,AB/48 (Item 48 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

06862775 91170750 PMID: 1672341
Inhibitors of ADP-ribose polymerase decrease the **resistance** of HER2/**neu** -expressing cancer cells to the cytotoxic effects of tumor necrosis factor.
Lichtenstein A; Gera J F; Andrews J; Berenson J; Ware C F
Department of Medicine, V.A. Wadsworth-UCLA Medical Center.
Journal of immunology (Baltimore, Md. : 1950) (UNITED STATES) Mar 15 **1991**, 146 (6) p2052-8, ISSN 0022-1767 Journal Code: 2985117R
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
Four human ovarian and breast tumor lines expressing the HER2/**neu** oncogene were **resistant** to the cytotoxic and DNA-degradative activity of TNF. The **resistance** was not associated with altered TNF receptor function because Scatchard analysis of 125I-rTNF binding to HER2/**neu** -expressing target cells revealed receptors with normal binding parameters. Furthermore, the TNF receptors on the **resistant** lines were capable of signal transduction as evidence by the induction of ADP-ribose polymerase activity and MHC expression. TNF **resistance** was not reversed by coincubation with drugs that interrupted the glutathione redox cycle. In addition, although coincubation of HER2/**neu** -expressing targets with cycloheximide resulted in significant TNF-induced lysis, when compared to HER2/**neu** -nonexpressing targets similarly treated with cycloheximide, a significant relative **resistance** was still present. To investigate the role of ADP-ribosylation in the **resistance** of these targets, we used nontoxic concentrations of two inhibitors of ADP-ribose polymerase, 3-aminobenzamide, and nicotinamide. Both inhibitors completely reversed the **resistance** of HER2/**neu** -expressing targets to TNF-mediated cytotoxicity and DNA injury in a concentration-dependent fashion. These inhibitors of ADP-ribose polymerase did not act by down-regulating expression of HER2/**neu** oncogenes. In contrast, aminobenzamide and nicotinamide significantly diminished TNF-induced cytotoxicity of L929 targets. These data suggest that the activity of ADP-ribose polymerase may play a pivotal role in determining the fate of the target cell during exposure to TNF.

4/3,AB/49 (Item 49 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

06644231 90341820 PMID: 2382147
Recent advances in the management of lung and breast cancer. Future directions.
Salmon S E
Arizona Cancer Center, University of Arizona College of Medicine, Tucson 85724.
Seminars in oncology (UNITED STATES) Aug **1990**, 17 (4 Suppl 7) p50-2, ISSN 0093-7754 Journal Code: 0420432
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
Since mortality from breast cancer remains unacceptably high, hopes for

future treatment depend, in large part, on the development of pharmacologic interventions based on an increased understanding of the biology of cancer. A fruitful area of exploration may be that of antisense RNAs which may inhibit the expression of a given growth factor or a given cellular product. It is also possible that an antisense RNA can be developed that will inhibit the production of proteins responsible for **drug resistance**. Another potential approach is the use of the **Her-2-Neu** oncogene cell membrane protein target for monoclonal antibody radioimmunoconjugates for therapy. Finally, since low-fat, reduced-calorie diets are considered an important part of preventive programs, the use of artificial fats may also make a significant difference in changing life-style habits.

4/3,AB/50 (Item 50 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

06501147 90206597 PMID: 2181373
Effect of glucocorticoids on oncogene transformed NIH3T3 cells.
Matin A; Cheng K L; Suen T C; Hung M C
Department of Tumor Biology, University of Texas, M.D. Anderson Cancer Center, Houston 77030.
Oncogene (ENGLAND) Jan **1990**, 5 (1) p111-6, ISSN 0950-9232 Journal Code: 8711562
Contract/Grant No.: CA-45265; CA; NCI
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed

We studied the differential response of oncogene transformed NIH3T3 cells to glucocorticoids. As demonstrated for transformed human fibroblasts, the morphology of **neu**-, ras-, src- and sis-transformed mouse fibroblasts became more normal after glucocorticoid treatment. This change was not due to inhibition of the expression of oncogene mRNA or protein. However, the abl-transformed NIH3T3 cells were **resistant** to glucocorticoid-induced morphology change. These results indicate that the glucocorticoid-induced morphology change is specific to certain oncogene-transformed NIH3T3 cells. Transformed human fibroblasts generally have reduced amounts of cell surface fibronectin. When treated with glucocorticoids, they incorporate higher levels of fibronectin in their extracellular matrix, which correlates with their change in morphology. However, we found that, except for abl-transformed cells, the fibronectin level of the other oncogene transformed mouse cells was similar to non-transformed cells. Moreover, treatment of the **neu** -, ras-, src- and sis-transformed cells with glucocorticoids resulted in a change in morphology but no increase in cell surface fibronectin. These studies demonstrate that the glucocorticoid-induced morphological change of oncogene-transformed NIH3T3 cells is not due to enhanced expression of fibronectin. Therefore, other mechanisms are responsible for this glucocorticoid-induced phenotypic change of oncogene-transformed cells.

4/3,AB/51 (Item 51 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

06456067 90153988 PMID: 1968062
Differential processing and turnover of the oncogenically activated **neu**/erb B2 gene product and its normal cellular counterpart.
Huang S S; Koh H A; Konish Y; Bullock L D; Huang J S
E.A. Doisy Department of Biochemistry and Molecular Biology, St. Louis University School of Medicine, Missouri 63104.
Journal of biological chemistry (UNITED STATES) Feb 25 **1990**, 265 (6) p3340-6, ISSN 0021-9258 Journal Code: 2985121R
Contract/Grant No.: CA-38808; CA; NCI

Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed

In nontransformed DHFR/G-8 cells (NIH 3T3 cells transfected with normal rat **neu** gene), the normal **neu** gene product was initially synthesized as a 170-kDa protein bearing endoglycosidase H-sensitive oligosaccharide chains and was then processed to a 175-kDa mature form with endoglycosidase H-**resistant**, endoglycosidase F-sensitive oligosaccharide chains. Most of this 175-kDa mature form appeared on the cell surface 2 h following synthesis and showed a half-life of approximately 3 h. In the presence of a growth factor(s) partially purified from bovine kidney, the half-life of this 175-kDa normal **neu** gene product was shortened to less than 30 min. In B104-1-1 cells (NIH 3T3 cells transfected with **neu** gene activated oncogenically by a point mutation that changes a valine residue to a glutamic acid residue in the putative transmembrane region), the oncogenically activated **neu** gene product was also synthesized as a 170-kDa precursor with endoglycosidase H-sensitive oligosaccharide chains. However, this 170-kDa precursor diminished very fast and was only partially processed to a 185-kDa mature form which exhibited a half-life of less than 30 min. The 185-kDa activated **neu** gene product possessed an unidentified post-translational modification in addition to N-linked oligosaccharide chains. Both the precursor and mature forms of the mutationally activated **neu** gene product showed increased tyrosine-specific phosphorylation as compared with those of their normal counterparts in DHFR/G-8 cells. The mutationally activated **neu** gene product in B104-1-1 cells shared several features which have been reported previously for the ligand-activated platelet-derived growth factor receptor in v-sis- or c-sis-transformed cells. These properties include: 1) accelerated turnover of the precursor and mature forms compared with the rates of turnover of its normal counterparts, 2) insensitivity of this rapid turnover to lysosomotropic amines, and 3) increased in vivo tyrosine-specific phosphorylation of both the precursor and mature forms. These findings suggest that the mutationally activated **neu** gene product may transform the cells by mimicking ligand-induced activation.

4/3,AB/52 (Item 52 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

05949826 89034458 PMID: 3053737

Antigenic and functional characterization of a rat central nervous system-derived cell line immortalized by a retroviral vector.

Geller H M; Dubois-Dalcq M
Department of Biology, University College, London, England.

Journal of cell biology (UNITED STATES) Nov **1988**, 107 (5) p1977-86, ISSN 0021-9525 Journal Code: 0375356
Contract/Grant No.: NS-25168; NS; NINDS
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed

We have immortalized rat central nervous system (CNS) cells of primary cultures of rat optic nerve with murine leukemia virus psi-2,SV-40-6, which is defective in assembly and contains the SV-40 large T antigen and neomycin **resistance** genes, to produce a cell line that we named A7. After **drug** selection, greater than 90% of the growing cells expressed nuclear SV-40 large T cells and a fraction of these contained the astrocyte-specific marker, glial fibrillary acidic protein. The majority of these cells also expressed surface marker A4 (specific for neural tube derivatives), Ran 2, p185 (the 185-kD phosphoprotein product of the **neu** oncogene), and fibronectin, but did not express the astrocyte enzymes glutamine synthetase and monoamine oxidase B. Surface markers

characteristic of glial progenitors (A2B5) and oligodendrocytes (galactocerebroside) were not detected. After two rounds of cell cloning, subclone A7.6-3 expressed Ran 2, fibronectin, and the neural cell adhesion molecule (N-CAM) but not glial fibrillary acidic protein and A4. The A7 cell line and subclones also displayed certain functions of type 1 astrocytes: the conditioned medium of these cells had a potent mitogenic activity for glial progenitor cells which could be neutralized by anti-platelet-derived growth factor antibodies and monolayers of these cells supported the growth of embryonic hypothalamic neurons. We conclude that a retrovirus containing SV-40 large T antigen can immortalize rat CNS cells and that such immortalized glial cells retain at least two important functions of type 1 astrocytes: the ability to secrete platelet-derived growth factor and to support the growth of embryonic CNS neurons. Moreover, such stable immortalized clonal cell lines can be used to study gene regulation in glial cells.

4/3,AB/53 (Item 53 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

04959773 86031371 PMID: 4054631
Use of the newer agents for antibiotic-**resistant** infection: Harold C. **Neu**, MD. Interview by Richard L. Peck.
Neu H C
Geriatrics (UNITED STATES) Nov **1985**, 40 (11) p100, 102-3, 106, ISSN 0016-867X Journal Code: 2985102R
Document type: Interview
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed

4/3,AB/54 (Item 54 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

04723139 85106747 PMID: 3855439
A lectinlike receptor on murine macrophage cell line cells, Mm1: involvement of sialic acid-binding sites in opsonin-independent phagocytosis for xenogeneic red cells.
Kyoizumi S; Masuda T
Journal of leukocyte biology (UNITED STATES) Mar **1985**, 37 (3) p289-304, ISSN 0741-5400 Journal Code: 8405628
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
The recognition mechanism of xenogenic red cells by mouse macrophages was studied by using established cell lines. Approximately 30% of cell line cells Mm1 which lack Ia antigen, as well as of thioglycollate-induced peritoneal macrophages from SL/Am mice (TGC-M phi) could ingest unopsonized quail red cells (QRC). In contrast, an undifferentiated type of cell line, M1-, and another type of macrophage cell line, Mk1-C, possessing accessory cell activity in association with the expression of Ia antigen, had no phagocytic activity for QRC. Approximately 80% of Mm1 cells, as well as TGC-M phi formed rosettes with QRC, whereas M1- and Mk1-C cells did not; indicating that specific binding sites for QRC are expressed on a large portion of Mm1 and TGC-M phi but not on M1- and Mk1-C cells. No requirement of divalent cation (Mg++, Ca++) and metabolic energy was observed for rosette formation between Mm1 cells and QRC. Protease treatment of Mm1 cells eliminated the rosetting activity, whereas periodate oxidation of glycosidase treatment slightly enhanced this activity, suggesting the involvement of surface protein in binding sites of Mm1 cells. In contrast to these findings on Mm1 cells, binding components of QRC were sensitive to periodate oxidation or neuraminidase treatment but **resistant** to

protease, suggesting that the terminal sialic acid residues of carbohydrate of QRC are recognized by Mm1 cells. Furthermore, N-acetylneuraminic acid (NeuNAc) inhibited the rosette formation and promoted the dissociation of rosettes already formed. N-Acetylneuramin lactose (**Neu**-NAc-Lact) was more efficient in rosette inhibition than NeuNAc. These sugars also blocked the phagocytosis of QRC by Mm1 cells but had no effect on either Fc-mediated phagocytosis or latex ingestion. These results suggest that phagocytosis of QRC by murine macrophages is mediated by protease-sensitive binding sites recognizing terminal sialic acid residues of QRC in conjunction with additional carbohydrates.

4/3,AB/55 (Item 55 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

03157845 79227008 PMID: 462875
[Characteristics of the action of N-nitrosoethylurea in rat embryogenesis]
Osobennosti deistviia N-nitrozoetilmocheviny u krys v embriogeneze.
Aleksandrov V A
Voprosy onkologii (USSR) **1979**, 25 (6) p60-5, ISSN 0507-3758
Journal Code: 0413775
Document type: Journal Article ; English Abstract
Languages: RUSSIAN
Main Citation Owner: NLM
Record type: Completed
Based on the experiments with single intravenous injections of **NEU** in rats with definite pregnancy terms, it was found the embryos are especially sensitive to embryotoxic effects at the 3d--4th and 9th day, to teratogenic effects--at the 9th--14th day. The carcinogenic effect of NMU (20 mg/kg) is evident following the exposure, starting from the 11th day of embryogenesis, and the former is equally maximum during the subsequent terms until the end of the intrauterine period, their offsprings developing multiple tumors of the central and peripheral nervous systems. The sensitivity of rat embryos to NMU carcinogenic effect, contrary to the embryotoxic and teratogenic ones, showed no strict staging character. No correlation was noted between gross developmental defects and the appearance of tumors.

4/3,AB/56 (Item 1 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
(c) 2002 BIOSIS. All rts. reserv.

10357598 BIOSIS NO.: 199698812516
Overexpression of p185-c-erbB-2 in breast cancer cells confers increased **resistance** to Taxol via inhibition of apoptosis.
AUTHOR: Liu B; Ferrer E; McDonnell T; Sun D; Hung M-C; Yu D
AUTHOR ADDRESS: Univ. Tex. M.D. Anderson Cancer Cent., Houston, TX 77030** USA
JOURNAL: Proceedings of the American Association for Cancer Research Annual Meeting 37 (0):p335 **1996**
CONFERENCE/MEETING: 87th Annual Meeting of the American Association for Cancer Research Washington, D.C., USA April 20-24, 1996
ISSN: 0197-016X
RECORD TYPE: Citation
LANGUAGE: English
1996

4/3,AB/57 (Item 2 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
(c) 2002 BIOSIS. All rts. reserv.

10355540 BIOSIS NO.: 199698810458
Receptor tyrosine kinase expression as a modulator of cis-platinum **resistance** and sensitivity.
AUTHOR: Donato N J; Ling Y-H; Siddik Z; Perez-Soler R
AUTHOR ADDRESS: Dep. Bioimmunotherapy, Thoracic/Head Neck Oncology Clinical Investigation, Univ. Texas M.D. Anderson**USA
JOURNAL: Proceedings of the American Association for Cancer Research Annual Meeting 37 (0):p32 **1996**
CONFERENCE/MEETING: 87th Annual Meeting of the American Association for Cancer Research Washington, D.C., USA April 20-24, 1996
ISSN: 0197-016X
RECORD TYPE: Citation
LANGUAGE: English
1996

4/3,AB/58 (Item 3 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
(c) 2002 BIOSIS. All rts. reserv.

10243860 BIOSIS NO.: 199698698778
Cytotoxic effects of gemcitabine-containing regimens against human non-small cell lung cancer cell lines which express different levels of p185-**neu**.
AUTHOR: Tsai Chun-Ming(a); Chang Kuo-Ting; Chen Jeou-Yuan; Chen Yuh-Min; Chen Mei-Hui; Perng Reury-Perng
AUTHOR ADDRESS: (a)Dep. Med., Sch. Med., Natl. Yang-Ming Univ., Taipei 11217**Taiwan
JOURNAL: Cancer Research 56 (4):p794-801 **1996**
ISSN: 0008-5472
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: A novel pyrimidine analogue, gemcitabine, has been found to inhibit DNA replication and repair. We speculated that gemcitabine in combination with DNA-damaging agents might be more active against high- than low-p185-**neu** expressing non-small cell lung cancer (NSCLC) cells because the high-p185-**neu** expressors were proposed to posses a more effective DNA repair ability. We therefore compared the combination effects of gemcitabine plus cisplatin, gemcitabine plus etoposide, and cisplatin plus etoposide in a panel of 12 NSCLC cell lines. We also investigated the correlations between the level of p185-**neu** and the cytotoxicities of each single agent and the three combinations. We found that as single agents the cytotoxicities of cisplatin and etoposide but not gemcitabine were significantly correlated with the level of p185-**neu**. In contrast to the tight crossresistance between cisplatin and etoposide, gemcitabine demonstrated little cross-**resistance** to either etoposide or cisplatin. Both gemcitabine-containing combinations demonstrated equivalent or more active cytotoxicities compared to cisplatin plus etoposide, with gemcitabine plus cisplatin showing a greater synergistic activity which was effect (dose) dependent. The effect of cisplatin plus etoposide was not p185-**neu** related, whereas gemcitabine-containing regimens, especially gemcitabine plus cisplatin, had a greater cytotoxicity against the high- than the low-p185-**neu** expressors. Our findings indicate that gemcitabine in combination with cisplatin is active against NSCLC cells in vitro. The gemcitabine-cisplatin interaction is more active than the etoposide-cisplatin interaction in cells with high-p185-**neu** expression.

1996

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Set      Items   Description
S1        8030   NEU OR HER (W) 2 OR ERBB?3 AND (ANTISENS? OR RIBOZYM?)
S2        3783   S1 AND PY<1997
S3          91   S2 AND DRUG AND RESIST?
S4          67   RD (unique items)
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             8030  S1
             3783  S2
          4146766  DRUG
           775216  RESIST?
       S5     178  S1 NOT S2 AND DRUG AND RESIST?
? rd
...examined 50 records  (50)
...examined 50 records  (100)
...examined 50 records  (150)
...completed examining records
       S6     136  RD (unique items)
? t s6/3,ab/all

 6/3,AB/1     (Item 1 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

13798255   21958719   PMID: 11961663
  Adenovirus-E1A gene therapy enhances the in vivo sensitivity of Ewing's
sarcoma to VP-16.
  Zhou Rong-Rong; Jia Shu-Fang; Zhou Zhichao; Wang Yunfang; Bucana Corazon
D; Kleinerman Eugenie S
  Division of Pediatrics, The University of Texas M. D. Anderson Cancer
Center, Houston, Texas 77030, USA.
  Cancer gene therapy (England) May 2002, 9 (5) p407-13, ISSN
0929-1903  Journal Code: 9432230
  Document type: Journal Article
  Languages: ENGLISH
  Main Citation Owner: NLM
  Record type: Completed
  This study determined the effect of Ad-E1A gene therapy in vivo. TC71
cells (2 x 10(6)) injected subcutaneously into nude mice resulted in tumor
development (1-3 mm) 6 days later. Animals were then treated with Ad-E1A or
Ad-beta-gal (5 x 10(9) plaque-forming units) by intratumoral injection
twice weekly for 2 weeks. Animals received 8 mg/kg VP-16 given by
intraperitoneal injection daily for 5 days following the first week of
treatment with Ad-E1A or Ad-beta-gal. Control animals received no therapy
or VP-16 only after tumor cells were injected. When tumors exceeded 2 x 2
cm, the mice were sacrificed and the tumors underwent histologic and
immunohistochemical analysis. Tumors from mice treated with Ad-E1A plus
VP-16 were 9.6-fold smaller than those treated with VP-16 alone and
6.3-fold smaller than those treated with Ad-E1A alone. HER2/neu p185
protein expression decreased in all tumors that received Ad-E1A therapy.
TUNEL fluorescence staining revealed more apoptosis in the tumors from
animals treated with Ad-E1A plus VP-16 than in those from animals treated
with Ad-E1A alone, Ad-beta-gal plus VP-16, or VP-16 alone. These data
demonstrated that Ad-E1A gene therapy down-regulated HER2/neu
expression, increased tumor cell apoptosis induced by VP-16, and enhanced
tumor cell sensitivity to VP-16. Ad-E1A may have potential in the treatment
of relapsed drug-resistant Ewing's sarcoma.


 6/3,AB/2     (Item 2 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

13727550   22001026   PMID: 12006548
  Overexpression of HER-2/neu in uterine serous papillary
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cancer.
Santin Alessandro D; Bellone Stefania; Gokden Murat; Palmieri Michela; Dunn Donna; Agha Jamshed; Roman Juan J; Hutchins Laura; Pecorelli Sergio; O'Brien Timothy; Cannon Martin J; Parham Groesbeck P
Department of Obstetrics and Gynecology, Division of Gynecologic Oncology, University of Arkansas, Little Rock 72205-7199, USA.
Clinical cancer research : an official journal of the American Association for Cancer Research (United States) May 2002, 8 (5) p1271-9, ISSN 1078-0432 Journal Code: 9502500
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
PURPOSE: Uterine serous papillary carcinoma (USPC) is a highly aggressive variant of endometrial cancer and histologically similar to high-grade ovarian cancer. **HER-2/neu** , the transmembrane receptor encoded by the c-erbB2 gene, is overexpressed by immunohistology in approximately 25% of ovarian cancers. In this study, we have evaluated the expression of **HER-2/neu** in several fresh, established, paraffin-embedded, fixed USPCs. In addition, we have tested the sensitivity of USPC cells to Herceptin treatment. EXPERIMENTAL DESIGN: Ten consecutive USPC specimens were assessed by immunohistochemistry for the intensity of expression of **HER-2/neu** . In addition, three USPC cell lines were analyzed for expression of **HER-2/neu** by flow cytometry as well as for sensitivity to Herceptin-mediated, complement-dependent cytotoxicity, antibody-dependent cellular cytotoxicity (ADCC), and inhibition of cell proliferation. RESULTS: Eight of 10 (80%) of the USPCs assessed immunohistochemically for the intensity of expression of **HER-2/neu** stained heavily for **HER-2/neu** (2+ to 3+). Fresh and established primary USPC cell lines were found to express significantly more **HER-2/neu** receptor by flow cytometry (on the average, 10-fold greater) when compared with **HER-2/neu**-positive primary or established breast and ovarian cancer cell lines ($P < 0.001$). Importantly, although these USPC cell lines were **resistant** to chemotherapy in vivo and to natural killer- and complement-mediated cytotoxicity in vitro, they were found to be highly sensitive to Herceptin-mediated ADCC. USPC cell proliferation was also inhibited by Herceptin. A significant enhancement of ADCC was demonstrated when effector cells were exposed to low doses of IL-2 in vitro. Physiological concentrations of human serum IgG did not inhibit Herceptin-mediated ADCC against USPC. CONCLUSIONS: On the basis of these findings and previous reports showing a positive in vivo correlation between efficacy of Herceptin therapy and the level of **HER-2/neu** overexpression by tumor cells, we propose that Herceptin might be a novel and attractive therapeutic strategy in patients harboring chemotherapy-**resistant**, recurrent, or metastatic USPC.

6/3,AB/3 (Item 3 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

13711341 22262364 PMID: 12375030
Molecular characterization as a target for cancer therapy in relation to orphan status disorders (Review).
Stathopoulos G P
Department of Oncology, 2nd Medical Division, Hippokration Hospital, University of Athens, Greece.
Oncology reports (Greece) Nov-Dec 2002, 9 (6) p1257-9, ISSN 1021-335X Journal Code: 9422756
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: In Process
The long-term effort in investigating chemical methods to eliminate only

cancer cells has improved our knowledge and has led to the development of new drugs. The targets for cancer treatment may be large polymeric molecules such as DNA or microtubules as well as regulatory pathways for tumor development and cell survival preservation or tyrosine kinase activity. Examples of new agents are: trastuzumab (Herceptin), a humanized monoclonal antibody that blocks the **HER-2/neu** proto-oncogene in combination with cytotoxic agents, is used in a percentage of breast cancer patients; signal transduction inhibitor of abl tyrosine kinase STI 571 (Glivec) has been shown to be an active treatment for chronic myeloid leukemia and GISTs; epidermal growth factor receptors in certain tumors have been targeted with agents such as C225 (Cetuximab) and ZD 1839 (IRESSA); an adenosine deaminase analogue of deoxyadenosine, Cladribine (2-chloro-2 deoxy-adenosine) has shown high effectiveness in hairy-cell leukemia and the multitargeted antifolate (Premetrexed) and several vaccines have been studied and are in clinical trials for **resistant** cancers. These new **drug** developments represent a promising field for future cancer management.

6/3,AB/4 (Item 4 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

13633585 22247700 PMID: 12239347
Chaperone-dependent E3 ubiquitin ligase CHIP mediates a degradative pathway for c-ErbB2/**Neu**.
Xu Wanping; Marcu Monica; Yuan Xitong; Mimnaugh Edward; Patterson Cam; Neckers Len
Cell and Cancer Biology Branch, Center for Cancer Research, National Cancer Institute, Rockville, MD 20850; and Program in Molecular Cardiology, University of North Carolina, Chapel Hill, NC 27599.
Proceedings of the National Academy of Sciences of the United States of America (United States) Oct 1 2002, 99 (20) p12847-52, ISSN 0027-8424 Journal Code: 7505876
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: In Process
Overexpression of the transmembrane receptor tyrosine kinase ErbB2 is common in multiple malignancies, including breast and ovarian cancer. ErbB2 is **resistant** to degradation mediated by c-Cbl, the E3 ubiquitin ligase responsible for ligand-induced ubiquitination of ErbB1 (epidermal growth factor receptor). Because of its **resistance** to degradation, ErbB2 is the preferred dimerization partner for other members of the ErbB family, and its overexpression in vivo is associated with poor prognosis. We now show that the chaperone-binding ubiquitin ligase CHIP efficiently ubiquitinates and down-regulates ErbB2. CHIP expression shortens the half-life of both nascent and mature ErbB2 protein. In vitro ubiquitination assay shows that CHIP serves as a ubiquitin ligase for ErbB2, and both exogenously expressed and endogenous CHIP coprecipitate with the kinase. Furthermore, CHIP association with ErbB2 requires a chaperone intermediate and is increased by the chaperone-binding **drug** geldanamycin, a potent stimulator of ErbB2 ubiquitination and degradation. These data describe a previously unrecognized pathway, amenable to pharmacologic manipulation, that mediates ErbB2 stability.

6/3,AB/5 (Item 5 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

13575392 22197479 PMID: 12209684
Does HER2/**neu** expression provide prognostic information in patients with advanced urothelial carcinoma?
Gandour-Edwards Regina; Lara Primo N; Folkins Ann K; LaSalle Janine M; Beckett Laurel; Li Yueju; Meyers Frederick J; DeVere-White Ralph

Department of Pathology, School of Medicine, University of California Davis, 95817, USA. regina.gandour-edwards@ucdmc.ucdavis.edu
Cancer (United States) Sep 1 2002, 95 (5) p1009-15, ISSN 0008-543X Journal Code: 0374236
Contract/Grant No.: CA63265; CA; NCI; N01-CM17101; CM; NCI
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
BACKGROUND: Muscle-invasive urothelial carcinoma of the bladder is a highly lethal malignancy, particularly in the setting of locally advanced or metastatic disease. Prior reports of HER2/**neu** (c-erbB-2 or HER2) expression in bladder carcinoma have been mixed; therefore, its value in predicting metastasis or response to therapy has not been established in this tumor type. Thus, the authors evaluated a possible correlation between HER2 expression in patients with high-grade, muscle-invasive urothelial carcinoma of the bladder and outcome in patients who received paclitaxel-based chemotherapy. METHODS: Archival tumor tissues from patients with advanced urothelial carcinoma who were enrolled on two clinical trials of paclitaxel-based chemotherapy regimens were analyzed for HER2/**neu** expression by immunohistochemistry (IHC). The authors correlated HER2 expression by IHC with clinical outcomes, such as response rate, progression free survival, and overall survival, using univariate analysis. RESULTS: Thirty-nine tumor specimens were assessed for HER2 expression, most of which (70%) were collected from patients with metastatic disease. All were high-grade urothelial carcinomas (transitional cell carcinomas, Grade 3). Strong HER2 expression (2+/3+) was seen in 28 patients (71%). Patients with responding disease had an HER2 expression rate of 78%, similar to the rate seen in patients with stable disease (75%). In contrast, patients with progressive disease had an HER2 expression rate of 50%, although this difference did not reach statistical significance. However, univariate analysis showed that increased HER2 expression predicted an improvement in progression free and overall survival. When HER2 status was used as a dichotomous variable, tumors with positive HER2 expression did not have any association with response or with progression free survival; however, positive HER2 status was associated significantly with a decreased risk of death (P = 0.03). CONCLUSIONS: This study of HER2 expression in bladder carcinoma focused on patients who were treated prospectively in a standardized fashion, unlike prior studies that have evaluated banked, archival specimens. The authors confirmed the findings of others that high-grade, muscle-invasive urothelial carcinoma of the bladder has a significant rate of HER2 expression (71%). However, contrary to other reports, the current study found that HER2 expression in the context of paclitaxel-based chemotherapy decreased the risk of death significantly. Further research is warranted on the possible association of HER2 expression with chemosensitivitiy in urothelial carcinoma as well as the efficacy of HER2-targeted therapies (such as trastuzumab) for patients with high-grade, muscle-invasive urothelial carcinoma of the bladder.
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6/3,AB/6 (Item 6 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

13524042 21873359 PMID: 11881914
Factors associated with success of the extreme **drug resistance** assay in primary breast cancer specimens.
Ellis Robert J; Fabian Carol J; Kimler Bruce F; Tawfik Ossama; Mayo Matthew S; Decelis Carlos Rubin; Jewell William R; Connor Carol; Modrell Carol; Praeger Mark; McGinness Marilee; Mehta Rita; Fruehauf John P
Department of Internal Medicine, University of Kansas Medical Center, Kansas City 66160, USA.
Breast cancer research and treatment (Netherlands) Jan 2002, 71 (2) p95-102, ISSN 0167-6806 Journal Code: 8111104

Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed

The extreme **drug resistance** (EDR) assay has not been widely studied in the setting of non-metastatic breast cancer. We evaluated the feasibility of performing the assay in 144 primary breast tumor specimens from two institutions by determining the rate of successful tumor culture for assays, number of drugs evaluated per assay, and time from tumor biopsy to receipt of results. We also sought to determine factors that are associated with assay success. An exploratory analysis was performed to detect possible associations between estrogen receptor (ER), progesterone receptor (PR) and HER2/**NEU** over-expression and extreme **drug resistance** demonstrated by the assay for specific chemotherapeutic agents. Of 144 tumor specimens submitted, tumor was successfully cultured for assay in 101(70%) of cases. A median of five drugs was evaluated per assay (range 2-9). Results were obtained in a median of 8 days (range 2-29). Young age, high tumor grade, PR negativity, and higher tumor submission weight were predictive for a successful assay. EDR was observed in 7-15% of tumors to doxorubicin, cyclophosphamide, 5-fluorouracil (5FU) and mitoxantrone, but EDR to paclitaxel was observed in 35%. Extreme **drug resistance** to 5-FU was associated with negative ER and PR status. There was a trend toward association between EDR to paclitaxel and HER2/**NEU** over-expression. The EDR assay may be successfully performed in the majority of tumors, and assay results are available in a timely fashion such that adjuvant treatment **drug** selection could be guided by results. These results may be helpful for designing possible future trials that evaluate the assay's role in adjuvant chemotherapy selection.

6/3,AB/7 (Item 7 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

13513578 22144606 PMID: 12149644

Her2/**neu** induces all-trans retinoic acid (ATRA) **resistance** in breast cancer cells.

Tari Ana M; Lim Soo-Jeong; Hung Mien-Chie; Esteva Francisco J; Lopez-Berestein Gabriel
Department of Bioimmunotherapy, Section of Immunobiology and Drug Carriers, The University of Texas M.D. Anderson Cancer Center, Houston, Texas, TX 77030, USA.

Oncogene (England) Aug 8 2002, 21 (34) p5224-32, ISSN 0950-9232 Journal Code: 8711562
Contract/Grant No.: K23-CA82119; CA; NCI
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed

We observed that all-trans retinoic acid (ATRA) inhibited the growth of MCF-7 breast cancer cells, but not those transfected with HER2/**NEU** or its transactivating ligand HEREGULIN. This suggests that Her2/**neu** causes breast cancer cells to be **resistant** to the growth inhibitory effects of ATRA. To confirm this observation, MDA-MB-453 and BT-474 cells, which have high levels of Her2/**neu** and are **resistant** to ATRA, were incubated with the trastuzumab (Herceptin) antibody so that we could determine whether inhibition of the expression and function of Her2/**neu** would resensitize these cells to ATRA. Indeed, we found that MDA-MB-453 and BT-474 cells treated with trastuzumab were growth inhibitory by ATRA. We then determined whether Her2/**neu** uses Grb2 and Akt proteins to induce ATRA **resistance** . Liposome-incorporated Grb2 antisense oligonucleotides (L-Grb2) and a dominant negative (DN) AKT mutant were used to down-regulate Grb2 expression and inhibit Akt activity, respectively. When incubated with L-Grb2 or transfected with the DN AKT mutant, ATRA-**resistant**, Her2/**neu** -overexpressing cells became

sensitive to ATRA. Our results indicate that Her2/**neu** utilizes Grb2 and Akt proteins to induce ATRA **resistance** in breast cancer cells. ATRA sensitivity was also correlated with RARalpha protein levels since higher RARalpha protein levels were observed in cells in which the Her2/**neu** pathway was inhibited.

6/3,AB/8 (Item 8 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

13391544 22047722 PMID: 12051881
Regulation of estrogen target genes and growth by selective estrogen-receptor modulators in endometrial cancer cells.
Dardes R C; Schafer J MacGregor; Pearce S Timm; Osipo C; Chen B; Jordan V C
Department of Gynecology, Federal University of Sao Paulo, Sao Paulo, Brazil.
Gynecologic oncology (United States) Jun 2002, 85 (3) p498-506, ISSN 0090-8258 Journal Code: 0365304
Contract/Grant No.: CA89018-01; CA; NCI
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
OBJECTIVE:Tamoxifen has mixed agonist/antagonist activities, leading to tissue-specific estrogen-like actions and endometrial cancer. The purpose of this study was to evaluate the effects of antiestrogens on the growth of estrogen receptor (ER)-positive ECC-1 endometrial cancer cells in vitro and in vivo. METHODS: We performed growth studies and luciferase assays using ERE-tK and AP-1 reporters. ERalpha protein expression was measured by Western blot after antiestrogen treatments. We investigated the actions of antiestrogens on the transcription of the pS2 gene in situ measured by Northern blot and the actions of antiestrogens on the VEGF protein secreted by ELISA. ERalpha, ERbeta, EGFR, and HER2/**neu** mRNAs were determined by RT-PCR. Last, ECC-1 tumors were developed by inoculation of cells into ovariectomized athymic mice and treated with estradiol (E2), tamoxifen, raloxifene, and a combination. RESULTS: E2 induced cell proliferation while antiestrogens did not. E2 and raloxifene down regulated ERalpha protein; in contrast, 4OHT did not. ICI182,780 completely degraded the receptor. ECC-1 cells express ERbeta at insignificant levels. Luciferase assays did not show any induction in ERE- nor AP-1-mediated transcription by antiestrogens. E2 caused a concentration-dependent increase in pS2 mRNA but antiestrogens did not. E2 increased VEGF expression in a dose-dependent manner and antiestrogens blocked E2 action. E2 down regulated HER2/**neu** while 4OHT and raloxifene did not change HER2/**neu** levels compared to control. In addition, EGFR mRNA was down regulated by E2 but raloxifene did not change it. Tamoxifen and raloxifene did not promote tumor growth in vivo. However, raloxifene (1.5 mg daily) only partially blocked E2-stimulated growth. CONCLUSION: Tamoxifen and raloxifene are antiproliferative agents and antiestrogens in ECC-1 endometrial cells in vitro and in vivo. The observation that selective estrogen-receptor modulators do not down regulate EGFR and HER2/**neu** mRNA may provide a potential role for these oncogenes in the development of raloxifene- or tamoxifen-stimulated endometrial cancer. The ECC-1 cell line could provide important new clues about the evolution of **drug resistance** to tamoxifen and raloxifene.

6/3,AB/9 (Item 9 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

13352086 21682507 PMID: 11824879
Trastuzumab: designer **drug** or fashionable fad?
Freebairn A J; Last A J; Illidg T M

Wessex Cancer Centre, Southampton General Hospital, UK.
Clinical oncology (Royal College of Radiologists (Great Britain)) (England) 2001, 13 (6) p427-33, ISSN 0936-6555 Journal Code: 9002902
Document type: Journal Article; Review; Review, Tutorial
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
Trastuzumab (Herceptin) is the first monoclonal antibody to be approved for the treatment of a solid tumour and is directed against the c-erb-B2 receptor. c-erb-B2 is a member of the epidermal growth factor family and approximately 25% of breast cancers express such receptors, which appear to confer a poorer prognosis and may be an indicator of **resistance** to cytotoxic chemotherapy. This review assesses the mechanisms of action of trastuzumab, discusses the measurement of the **HER-2/neu** gene and its products, and describes the preclinical and clinical studies that have been instrumental to date in the emergence of trastuzumab in clinical practice.

6/3,AB/10 (Item 10 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

13347265 22101212 PMID: 12108894
The current status of docetaxel for metastatic breast cancer.
Esteva Francisco J
Department of Breast Medical Oncology, The University of Texas M.D. Anderson Cancer Center, Houston 77030, USA. festeva@mdanderson.org
Oncology (Williston Park, N.Y.) (United States) Jun 2002, 16 (6 Suppl 6) p17-26, ISSN 0890-9091 Journal Code: 8712059
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: In Process
Docetaxel (Taxotere) has been intensively investigated for the treatment of metastatic breast cancer, where it has proved to be one of the most active agents. Initial phase II studies in anthracycline-**resistant** metastatic breast cancer demonstrated impressive response rates that have been confirmed in phase III randomized trials. Docetaxel remains the only single agent to demonstrate a survival benefit in anthracycline-**resistant** patients. More recently, the combination of docetaxel with capecitabine (Xeloda) has demonstrated additional improvement in survival over docetaxel alone in a randomized phase III trial. In patients previously treated with an alkylating agent, docetaxel is the only single **drug** to demonstrate improved efficacy over doxorubicin in a randomized trial. Docetaxel has been investigated in combination with the anthracyclines doxorubicin and epirubicin in randomized trials. The docetaxel-containing regimens have consistently demonstrated improvement over the non-docetaxel-containing regimens. The efficacy and safety of weekly docetaxel has extended the line of investigation for combinations with agents normally administered on a weekly basis, such as vinorelbine [Navelbine], gemcitabine [Gemzar], and trastuzumab [Herceptin], with promising findings. In addition, the results of the triple-**drug** combination of docetaxel, a platinum salt (cisplatin or carboplatin), and trastuzumab have resulted in impressive response rates and time to progression in a population of metastatic breast cancer patients with HER2/ **neu** -positive tumors. The consistent demonstration of a high level of efficacy with manageable toxicity ensures the continued widespread investigation of docetaxel in metastatic breast cancer.

6/3,AB/11 (Item 11 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

13302539 21913058 PMID: 11916237

Inhibition of erbB receptor (HER) tyrosine kinases as a strategy to abrogate antiestrogen **resistance** in human breast cancer.

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Languages: ENGLISH

Main Citation Owner: NLM

Record type: Completed

It has been proposed that binding of ligand to the estrogen receptor (ER) releases its association with transcriptional corepressors, allowing the ER to recruit coactivators, which possess histone acetylase activity, and induce transcription of gene promoters containing estrogen response elements. It has also been proposed that the antiestrogen tamoxifen recruits transcriptional corepressors to the AF-2 region of the hormone-binding domain of the ER, thus blocking ER-mediated transcription. The ER cross-talks with a number of mitogenic signaling pathways and second messengers, like the epidermal growth factor receptor, the insulin-like growth factor-I receptor, mitogen-activated protein (MAP) kinase, phosphatidylinositol-3 kinase/Akt, dopamine, and cyclic AMP. Some of these molecules may: (a) support ligand-independent ER transcription; (b) increase the association of ER with coactivators of transcription; and/or (c) reduce the antiestrogen-induced association of ER with corepressors. These events either alone or in combination may result in hormone independence and/or antiestrogen **resistance**. We have examined whether signaling by HER2/**neu** (erbB-2) receptor tyrosine kinase, which can induce antiestrogen **resistance** , can also disrupt the tamoxifen-induced interaction of ER with transcriptional corepressors. Notably, tamoxifen-induced association of ER with the transcriptional corepressors N-CoR or SMRT was reduced in HER2-overexpressing breast tumor cells but not in cells with low HER2 levels. Small molecule inhibitors of the HER2 kinase or MAP extracellular signal-regulated kinase 1/2 or dominant-negative MAP extracellular signal-regulated kinase 1/2 constructs restored the inhibitory effect of tamoxifen on both ER-mediated transcription and tumor cell proliferation. Treatment with both tamoxifen and the small molecule HER1/2 kinase inhibitor AG1478 reduced mitogen-activated protein kinase activity and markedly reduced growth of established MCF-7/HER2 xenografts in athymic nude mice. Similar results have been obtained with ZD1839 ("Iressa"), an epidermal growth factor receptor (HER1) tyrosine kinase inhibitor. Taken together, these data suggest that exogenous inhibitors of the HER-signaling network and other mitogenic pathways can abrogate or delay the emergence of antiestrogen **resistance**, thus providing an evaluable therapeutic strategy in human breast carcinoma.

6/3,AB/12 (Item 12 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

13168504 21970113 PMID: 11973639

Squalamine and cisplatin block angiogenesis and growth of human ovarian cancer cells with or without **HER-2** gene overexpression.

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Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed

Angiogenesis is important for growth and progression of ovarian cancers. Squalamine is a natural antiangiogenic sterol, and its potential role in treatment of ovarian cancers with or without standard cisplatin chemotherapy was assessed. Since **HER-2** gene overexpression is associated with cisplatin **resistance** in vitro and promotion of tumor angiogenesis in vivo, the response of ovarian cancer cells with or without **HER-2** gene overexpression to squalamine and cisplatin was evaluated both in tumor xenograft models and in tissue culture. Ovarian cancer cells with or without **HER-2** overexpression were grown as subcutaneous xenografts in nude mice. Animals were treated by intraperitoneal injection with control vehicle, cisplatin, squalamine or cisplatin combined with squalamine. At the end of the experiment, tumors were assessed for tumor growth inhibition and for changes in microvessel density and apoptosis. Additional in vitro studies evaluated effects of squalamine on tumor and endothelial cell growth and on signaling pathways in human endothelial cells. Profound growth inhibition was elicited by squalamine alone and by combined treatment with squalamine and cisplatin for both parental and **HER-2** -overexpressing ovarian tumor xenografts. Immunohistochemical evaluation of tumors revealed decreased microvessel density and increased apoptosis. Although **HER-2** -overexpressing tumors had more angiogenic and less apoptotic activity than parental cancers, growth of both tumor types was similarly suppressed by treatment with squalamine combined with cisplatin. In in vitro studies, we found that squalamine does not directly affect proliferation of ovarian cells. However, squalamine significantly blocked VEGF-induced activation of MAP kinase and cell proliferation in human vascular endothelial cells. The results suggest that squalamine is anti-angiogenic for ovarian cancer xenografts and appears to enhance cytotoxic effects of cisplatin chemotherapy independent of **HER-2** tumor status.

6/3,AB/13 (Item 13 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

13146775 21957089 PMID: 11960379

Identification of signal transduction pathways involved in constitutive NF-kappaB activation in breast cancer cells.

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Oncogene (England) Mar 27 2002, 21 (13) p2066-78, ISSN 0950-9232
Journal Code: 8711562
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed

Nuclear factor-kappaB (NF-kappaB) is usually maintained in an inactive form in the cytoplasm through its association with inhibitor of kappaB (IkappaB) proteins, and is activated upon stimulation of cells with a variety of signals. However, constitutive activation of NF-kappaB is observed in a number of cancers including breast cancer. The signaling pathways that are involved in constitutive NF-kappaB activation remain largely unknown. Using breast cancer cell lines derived from transgenic mice that overexpress specific oncogene/growth factors in the mammary gland, we show that heregulin but not her2/**neu**, c-Myc or v-Ha-ras plays a major role in constitutive NF-kappaB activation. Her2/**neu** potentiated tumor necrosis factor alpha (TNFalpha)-inducible NF-kappaB activation whereas c-Myc potentiated 12-o-tetracecanyolphorbol-13-acetate (TPA)-induced NF-kappaB activation. Heregulin-mediated NF-kappaB activation correlated with phosphorylation of epidermal growth factor receptor (EGFR)

and ErbB3 but not her2/**neu** . Tryphostin AG1517, which inhibits heregulin-mediated phosphorylation of EGFR, her2/**neu** and ErbB3 reduced NF-kappaB activation. In contrast, emodin, which blocks phosphorylation of her2/**neu** by heregulin, failed to reduce NF-kappaB activation. These results suggest that heregulin induces NF-kappaB independent of her2/**neu**. PI3 kinase/AKT, protein kinase A (PKA) and IkappaB kinase appear to be downstream signaling molecules involved in NF-kappaB activation as specific inhibitors of these kinases but not inhibitors of ERK/MAP kinase or protein kinase C reduced heregulin-mediated NF-kappaB activation. Based on these results, we propose that heregulin increases the expression of pro-invasive, pro-metastatic and anti-apoptotic genes in cancer cells through autocrine activation of NF-kappaB, which leads to invasive and **drug-resistant** growth of breast cancer.

6/3,AB/14 (Item 14 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

13006255 21897246 PMID: 11899388
Taxanes for breast cancer: an evidence-based review of randomized phase II and phase III trials.
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Clin Breast Cancer (United States) Apr 2000, 1 (1) p32-40; discussion 41-2, ISSN 1526-8209 Journal Code: 100898731
Document type: Journal Article; Review; Review, Tutorial
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
The taxanes paclitaxel and docetaxel have an important role in the treatment of breast cancer, and numerous randomized trials have evaluated their efficacy for this indication. A systematic, evidence-based review was performed, which included all randomized, controlled trials evaluating taxanes for the treatment of early-or advanced-stage breast cancer that were identified in CANCERLIT and MEDLINE searches. The primary objectives of this review were to determine the dose and schedule for each taxane that was associated with the most favorable therapeutic index, and to determine whether (and under what circumstances) the taxanes improved survival. The search revealed 18 randomized phase II (n = 1) or phase III (n = 17) trials. For metastatic breast cancer, the dose and schedule associated with the most favorable therapeutic index for paclitaxel was 175 mg/m2 given as a 3-hour infusion every 3 weeks, and docetaxel was 60-100 mg/m2 given as a 1-hour infusion every 3 weeks. Survival was improved under the following circumstances: (1) when 4 cycles of paclitaxel (175 mg/m2 every 3 weeks) was given following 4 cycles of conventional doxorubicin-cyclophosphamide for axillary node-positive operable breast cancer, (2) when trastuzumab was added to paclitaxel as first-line therapy for metastatic breast cancer that overexpressed HER2/**neu** , and (3) when docetaxel was given as second-line therapy for anthracycline-**resistant** disease. Although a survival benefit was found for taxanes as a component of first-line therapy in two of six trials, the interpretation of both positive trials was confounded by a lack of crossover to taxane therapy in those who were initially randomized to receive standard therapy. The taxanes improve survival in patients with early-stage breast cancer and selected patients with metastatic breast cancer. Further research is necessary in order to identify the efficacy of docetaxel relative to paclitaxel, the optimal dose of docetaxel, the role of weekly taxane therapy, the role of trastuzumab plus taxanes in early-stage disease, and whether taxanes are more effective when given concomitantly or sequentially in patients with early-stage disease.

6/3,AB/15 (Item 15 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

13006233 21897657 PMID: 11899784
HER2/**neu** as a predictive factor in breast cancer.
Lohrisch C; Piccart M
Investigational Drug Branch for Breast Cancer, European Organization for Research and Treatment of Cancer, Brussels, Belgium.
Clin Breast Cancer (United States) Jul 2001, 2 (2) p129-35; discussion 136-7, ISSN 1526-8209 Journal Code: 100898731
Document type: Journal Article; Review; Review, Tutorial
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
One of the current trends in breast cancer research is to identify markers that can predict response to specific anticancer therapies; intense laboratory research and therapeutic trials are exploiting this strategy. The combination of cytotoxic drugs directed at the tumor population with the highest probability of being sensitive to them with molecules targeted at intracellular signaling and cell cycle control pathways, which may be deregulated as part of the malignant process, represents our best hope for improved survival in both early and advanced disease. The transmembrane tyrosine kinase receptor, HER2/**neu** , has been the subject of much investigation with respect to its prognostic value, predictive value, and as a target of antibody-mediated therapy. Retrospective evidence strongly suggests that HER2 overexpression is associated with decreased disease-free and overall survival in node-positive, and possibly also node-negative, breast cancer. Prospective trials have demonstrated that antibodies to HER2 can produce tumor responses in women with advanced disease that overexpresses this molecule. Moreover, the combination of such antibodies with cytotoxic drugs has been one of the few recent strategies to improve survival duration in metastatic breast cancer. The evidence supporting the role of HER2 as a factor predictive of response to hormone therapy and cytotoxic drugs is more ambiguous and requires prospective assessment. The available literature is reviewed herein, with a focus on the predictive value of HER2, potential mechanisms of **resistance** and sensitivity to various drugs, and future research directions involving this important molecule.

6/3,AB/16 (Item 16 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

13005369 21896897 PMID: 11900227
HER-2/neu overexpression is rare in hepatocellular carcinoma and not predictive of anti-**HER-2/neu** regulation of cell growth and chemosensitivity.
Hsu Chiun; Huang Chin-Lun; Hsu Hey-Chi; Lee Po-Huang; Wang Shiou-Jeng; Cheng Ann-Lii
Department of Oncology, National Taiwan University Hospital, Taipei.
Cancer (United States) Jan 15 2002, 94 (2) p415-20, ISSN 0008-543X Journal Code: 0374236
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
BACKGROUND: The overexpression of **HER-2/neu** oncogene has been implicated in the development and modulation of many types of cancer. However, whether **HER-2/neu** overexpression plays a similar role in hepatocellular carcinoma (HCC) has not been determined. METHODS: Tissue specimens from 36 HCC patients who had been enrolled in 3 separate prospective clinical trials of systemic chemotherapy were studied by immunohistochemical staining. A polyclonal antibody (A0485; DAKO, Copenhagen, Denmark) against **HER-2/neu** and a horseradish

peroxidase-based visualization system (Envision+, DAKO) was used. Scoring criteria was in accordance with the manufacturer's guidelines. Twelve HCC cell lines were examined for **HER-2/neu** overexpression by Western blotting. Single-agent growth regulatory activity of the anti-**HER-2/neu** antibody, trastuzumab (Herceptin; Genentech, South San Francisco, CA), and its combinative cytotoxicity with chemotherapeutic agents (doxorubicin, gemcitabine, cisplatin, irinotecan) were determined by a tetrazolium-based colorimetric assay (MTT test). RESULTS: All but one of the HCC tumor tissues were negative for **HER-2/neu** expression. The only patient with positive **HER-2/neu** expression was a 57-year-old male patient who achieved stabilization of disease for 2 months after chemotherapy. Eight of the 35 patients with negative **HER-2/neu** expression had had partial remission after chemotherapy (P = 0.78). Only one (Tong cells) of the 12 HCC cell lines had a significant level of **HER-2/neu** expression. However, trastuzumab up to 10 microg/mL had no discernible growth inhibitory or chemosensitizing effect on Tong cells or any other cell lines. CONCLUSIONS: **HER-2/neu** overexpression is rare in human HCC tissues, and anti-**HER-2/neu** regulation appears to play little role in the treatment of this tumor.

6/3,AB/17 (Item 17 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

12998306 21891330 PMID: 11894015
Trastuzumab in the treatment of non-small cell lung cancer.
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Department of Thoracic Oncology Service, Memorial Sloan-Kettering Cancer Center, New York, NY 10021, USA.
Seminars in oncology (United States) Feb 2002, 29 (1 Suppl 4) p59-65, ISSN 0093-7754 Journal Code: 0420432
Document type: Journal Article; Review; Review, Tutorial
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
Trastuzumab is a humanized monoclonal antibody that binds to human epidermal growth factor-2 (HER2) and is approved by the US Food and **Drug** Administration for the treatment of advanced breast cancer that overexpresses HER2/**neu** protein. Preclinical data suggests a role for trastuzumab in the treatment of non-small cell lung cancer (NSCLC). HER2 protein is overexpressed in 20% to 66% of resected NSCLC tumors, and has been shown to predict poor patient outcome in multiple series. Experiments with NSCLC cell lines show that HER2 overexpression increases chemoresistance, invasiveness, and metastatic potential of the cells. In mouse xenograft experiments, trastuzumab halts tumor growth and is synergistic with cytotoxic chemotherapy. Ongoing phase II trials are showing that trastuzumab can be added to standard chemotherapy in the treatment of patients with advanced NSCLC without additional toxicity, and with promising efficacy. Whether trastuzumab will show a clear benefit for patients with NSCLC, either alone or in combination with established chemotherapy, remains to be proven in phase III testing.

6/3,AB/18 (Item 18 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

12995773 21595267 PMID: 11759828
HER-2/neu overexpression and in vitro chemosensitivity to CMF and FEC in primary breast cancer.
Konecny G; Fritz M; Untch M; Lebeau A; Felber M; Lude S; Beryt M; Hepp H; Slamon D; Pegram M

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Breast cancer research and treatment (Netherlands) Sep 2001, 69 (1) p53-63, ISSN 0167-6806 Journal Code: 8111104
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
Available clinical and experimental data on the effect of **HER-2/neu** overexpression on chemosensitivity are controversial. It was the purpose of this in vitro study to define the association between **HER-2/neu**· overexpression and the sensitivity to the chemotherapeutic **drug** combinations of cyclophosphamide, methotrexate and 5-fluorouracil (CMF) and 5-fluorouracil, epirubicin and cyclophosphamide (FEC) of breast cancer cells derived from 140 chemotherapy-naive patients at the time of primary surgery. Both **drug** combinations were tested at six different concentrations ranging from 6.25-200% peak plasma concentration (PPC). Immunohistochemical detection of **HER-2/neu** overexpression was performed with the **HER-2/neu** antibodies, CB11, TAB250 and AO485, in the same tumor specimens. Immunoreactions were determined as negative (0/1+), weakly positive (2+) and strongly positive (3+). However, the antibodies varied in their degrees of sensitivity. Breast cancer samples with strong (3+) **HER-2/neu** overexpression demonstrated 90% growth inhibition (IC90) at significantly lower PPC values, using the CB11 ($p = 0.048$), TAB250 ($p = 0.007$) and AO485 ($p < \text{or} = 0.01$) antibodies, and showed 50% growth inhibition (IC50) at significantly lower PPC values, using the CB11 antibody ($p = 0.01$) compared to their counterparts with lower levels of **HER-2/neu** expression. When analyzing the group of patients with intermediate and strong **HER-2/neu** overexpression (2+ and 3+), an association between **HER-2/neu** overexpression and increased chemosensitivity was seen with the TAB250 ($p = 0.044$) and AO485 ($p = 0.032$) antibodies, but not with the CB11 antibody ($p = 0.8$) at the IC90 level. Differences in chemosensitivity between samples with strong **HER-2/neu** overexpression and those with lower levels were then analyzed separately for CMF and FEC. Both regimens achieved 90% tumor growth inhibition at lower PPC values in samples with strong **HER-2/neu** overexpression (3+) compared to their counterparts with lower expression levels (AO485 $p = 0.011$ for CMF, and $p = 0.09$ for FEC). Cumulative concentration-response plots of tumors responding in vitro with 90% tumor cell inhibition showed a stronger dose dependence for both CMF and FEC among tumor samples with strong **HER-2/neu** overexpression compared to those with lower levels of expression. In conclusion, the data show that **HER-2/neu** overexpression was not associated with in vitro **drug resistance** to CMF or FEC. In contrast, tumors with strong **HER-2/neu** overexpression demonstrated increased dose-dependent in vitro sensitivity to both the FEC and CMF regimens.

6/3,AB/19 (Item 19 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

12851413 21650954 PMID: 11791182
Differential sensitivity of cancer cells to inhibitors of the epidermal growth factor receptor family.
Bishop Philippe C; Myers Timothy; Robey Robert; Fry David W; Liu Edison T ; Blagosklonny Mikhail V; Bates Susan E
Medicine Branch, NCI, NIH, Bethesda, Maryland, MD 20892, USA, and FDA/CBER/OTRR/DCTDA/Oncology Branch, HFM-573, Rockville, Maryland, MD 20852, USA.
Oncogene (England) Jan 3 2002, 21 (1) p119-27, ISSN 0950-9232 Journal Code: 8711562
Document type: Journal Article

Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
Clinical responses to the HER1 (EGF receptor) inhibitors and HER2/**neu** /ErbB2 inhibitors correlate with high levels of receptor expression. However, a significant subset of patients with high receptor levels appear to be refractory to treatment. We have observed similar results in the 60 cell lines of the NCI Anti-Cancer **Drug** Screen using a panel of 11 selective HER1 inhibitors. As expected, low HER1-expressing cell lines were insensitive to HER1 inhibitors. In cell lines with high HER1 expression, low concentrations of HER1 inhibitors potently inhibit both HER1 phosphorylation and the mitogen-activated protein kinase (MAPK) pathway. However, this inhibition did not always correlate with cellular arrest. High HER1-expressing cell lines can be subdivided into two groups based on their sensitivity to HER1 inhibitors. In the sensitive group, receptor and growth inhibition was concordant and occurred at sub-micromolar concentrations of HER1 inhibitors. In the insensitive group, receptor inhibition occurred at a low concentration (< 1 microM) but concentrations that were ten times or higher were required for growth inhibition. Also, neither induction of p21 and cyclin D1 nor p53 status could explain the difference between sensitive and insensitive cells. Although EGF activated the MAPK pathway in all cell lines, only **drug** -sensitive cell lines responded to EGF (accelerated entry from G1 to S) and to HER1 inhibitors (G1 arrest) by changes in cell cycling. Furthermore, an EGF-dependent immortalized mammary epithelial cell line was extremely sensitive to a panel of HER1 inhibitors. We infer that independence from mitogen-mediated signaling confers insensitivity to HER1 inhibitors in a large subset of cancer cell lines.

6/3,AB/20 (Item 20 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

12770617 21634698 PMID: 11774281
Resistance to tamoxifen-induced apoptosis is associated with direct interaction between Her2/**neu** and cell membrane estrogen receptor in breast cancer.
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International journal of cancer. Journal international du cancer (United States) Jan 20 2002, 97 (3) p306-12, ISSN 0020-7136 Journal Code: 0042124
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
Overexpression of Her2/**neu** is implicated in the development of **resistance** to the antiestrogen tamoxifen (TAM) that exerts its inhibitory effect through interaction with estrogen receptor (ER). Whereas Her2/**neu** and ER are believed to be important cell survival/death factors in human breast cancer cells, if and how they interact to confer **resistance** to hormone therapy is not known. This prompted us to investigate whether modulation of the effect of TAM occurs via the Her2/**neu** pathway and whether targeting the interaction between the Her2/**neu** pathway and the ER pathway is beneficial. There are 2 forms of ER that are localized to the cell membrane and to the nucleus. For the first time, we found that Her2/**neu** directly interacts with ER at the cell membrane. We then investigated the role of Her2/**neu** overexpression in the regulation of the cell membrane ER pathway in TAM-**resistant** breast cancer cells and the nature of this interaction in apoptotic signaling. Relief of TAM **resistance** was associated with Her2/**neu** downregulation and ER upregulation. TAM-induced apoptosis

occurred immediately after dissociation of Her2/**neu** from cell membrane ER. These results demonstrate a novel mechanism by which Her2/**neu** regulates the cell membrane ER-coupled apoptosis and the possible involvement of the Her2/**neu** in TAM **resistance** of breast cancer cells. Moreover, the antiproliferative activity of TAM should rely on the integration between the signal transduction from the cell membrane ER and the gene regulation by the nuclear ER. Coordinated modulation on the cell membrane ER/Her2/**neu** pathway and the nuclear ER/RAR pathway may provide a new approach for treatment of ER-positive, Her2/**neu** overexpressing breast cancer. Copyright 2001 Wiley-Liss, Inc.

6/3,AB/21 (Item 21 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

12770238 21633131 PMID: 11776572
Expression and clinical significance of telomerase catalytic subunit gene in lung cancer and its correlations with genes related to **drug resistance** and apoptosis]
Wang J; Liu X; Fang J
Department of Internal Medicine, School of Oncology, Beijing Medical University, Beijing 100036.
Zhonghua zhong liu za zhi Chinese journal of oncology (China) Sep 1999, 21 (5) p350-3, ISSN 0253-3766 Journal Code: 7910681
Document type: Journal Article ; English Abstract
Languages: CHINESE
Main Citation Owner: NLM
Record type: Completed
OBJECTIVE: To investigate mRNA expression and prognostic significance of telomerase catalytic subunit (hTRT/hEST2) and its relations to apoptosis, proliferation and **drug resistance** in patients with lung cancer.
METHODS: Telomerase repeat amplification protocol-PCR(TRAP-PCR) and in situ hybridization were used to detect telomerase activity and expression of hTRT/hEST2 mRNA, respectively. The expression of bcl-2, c-myc, MRP, **Neu** , MDR1 at mRNA and protein levels was measured by means of RT-PCR and immunohistochemisty. In situ end labeling(ISEL) assay was used to evaluate apoptotic cells. RESULTS: hTRT/hEST2 mRNA was detected in 41 of 56 NSCLC(73.2%) and 17 of 20 SCLC(85.0%), but it was not expressed in lung tissues adjacent to the tumor. Telomerase activity was postively correlated with the expression of hTRT/hEST2. In NSCLC, hTRT/hEST2 mRNA was positively correlated with bcl-2($r = 0.7327$, $P = 0.015$), c-myc($r = 0.8263$, $P = 0.001$), MRP($r = 0.3971$, $P = 0.003$) and **neu**($r = 0.3208$, $P = 0.017$), but not with MDR1 ($r = 0.2415$, $P = 0.672$). In SCLC, positive correlation was only found between hTRT/hEST2 and bcl-2 ($r = 0.5663$, $P = 0.024$). Correlation was positive between hTRT/hEST2 mRNA and Ki-67 expression but negative between hTRT/hEST2 and apoptosis both in NSCLC and SCLC. Multivariate Cox regression analysis showed that telomerase catalytic subunit hTRT/hEST2 and number of apoptotic cells were of prognostic significance in NSCLC. CONCLUSION: As telomerase catalytic subunit expression shows correlations with MDR- and apoptosis-related genes and is of prognostic significance, telomerase in relation to multiple **drug resistance** deserves in-depth study.

6/3,AB/22 (Item 22 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

12765744 21623989 PMID: 11752009
Insulin-like growth factor-I receptor signaling and **resistance** to trastuzumab (Herceptin).
Lu Y; Zi X; Zhao Y; Mascarenhas D; Pollak M
Department of Oncology, Jewish General Hospital, and McGill University, Montreal, PQ, Canada.
Journal of the National Cancer Institute (United States) Dec 19 2001,

93 (24) p1852-7, ISSN 0027-8874 Journal Code: 7503089
Comment in J Natl Cancer Inst. 2001 Dec 19;93(24) 1830-2; Comment in PMID 11752000
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
BACKGROUND: Trastuzumab (Herceptin), an anti-HER2/**neu** receptor monoclonal antibody that inhibits growth of ErbB2-overexpressing breast cancer, is used to treat such cancers. Development of **resistance** to trastuzumab, however, is common. We investigated whether insulin-like growth factor-I (IGF-I), which activates cell survival signals, interferes with the growth-inhibitory action of trastuzumab. METHODS: MCF-7/HER2-18 and SKBR3 human breast cancer models were used to assess cell proliferation, colony formation in soft agar, and cell cycle parameters. Throughout, we used trastuzumab at a dose of 10 microg/mL and IGF-I at a dose of 40 ng/mL. All statistical tests were two-sided. RESULTS: Trastuzumab inhibited the growth of MCF-7/HER2-18 cells, which overexpress HER2/**neu** receptors and express IGF-I receptors (IGF-IRs), only when IGF-IR signaling was minimized. For example, in 1% fetal bovine serum (FBS), trastuzumab reduced cell proliferation by 42% (P =.002); however, in 10% FBS or IGF-I, trastuzumab had no effect on proliferation. In SKBR3 cells, which overexpress HER2/**neu** receptor but express few IGF-IRs, trastuzumab reduced proliferation by 42% (P =.008) regardless of IGF-I concentration. When SKBR3 cells were genetically altered to overexpress IGF-IRs and cultured with IGF-I, trastuzumab had no effect on proliferation. However, the addition of IGF-binding protein-3, which decreased IGF-IR signaling, restored trastuzumab-induced growth inhibition. CONCLUSIONS: In breast cancer cell models that overexpress HER2/**neu**, an increased level of IGF-IR signaling appears to interfere with the action of trastuzumab. Thus, strategies that target IGF-IR signaling may prevent or delay development of **resistance** to trastuzumab.

6/3,AB/23 (Item 23 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

12686802 21587747 PMID: 11731427
HER-2 amplification impedes the antiproliferative effects of hormone therapy in estrogen receptor-positive primary breast cancer.
Dowsett M; Harper-Wynne C; Boeddinghaus I; Salter J; Hills M; Dixon M; Ebbs S; Gui G; Sacks N; Smith I
Breast Unit, Royal Marsden Hospital, London, United Kingdom. mitch@icr.ac.uk
Cancer research (United States) Dec 1 2001, 61 (23) p8452-8, ISSN 0008-5472 Journal Code: 2984705R
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
In experimental models, human epidermal growth factor receptor-2 (**HER-2**) amplification leads to estrogen independence and tamoxifen **resistance** in estrogen receptor (ER)-positive human breast cancer cells. Some but not all reports suggest an association between **HER-2** positivity and hormone independence in breast cancer patients. This study aimed to evaluate the antiproliferative effects of endocrine therapy in **HER-2**-positive/ER-positive primary human breast cancer. The effect on proliferation (Ki67) of hormone therapy was assessed at 2 weeks and/or 12 weeks in biopsies from 115 primary breast cancers with ER-positive tumors. The patients took part in one of 3 neoadjuvant trials of hormonal therapy with a SERM (tamoxifen or idoxifene) or an aromatase inhibitor (anastrozole or vorozole). **HER-2** status was assessed by immunocytochemistry and fluorescence in situ hybridization (FISH). Fifteen patients were defined as **HER-2**

positive by both immunohistochemistry and FISH, with the remaining 100 patients **HER**-**2** negative. Geometric mean Ki67 levels were substantially higher in **HER**-**2**-positive than **HER**-**2** -negative tumors (27.7% versus 11.5%, respectively; P = 0.003). In **HER**-**2** -negative patients, Ki67 was reduced by 62 and 71% at 2 and 12 weeks, respectively (P < 0.0001 for both), but **HER**-**2** -positive patients showed no significant fall. The proportional change in Ki67 was significantly different between **HER**-**2**-positive and -negative patients (P = 0.014 at 2 weeks; P = 0.047 at 12 weeks). Mean ER levels were lower in the **HER**-**2**-positive patients (P = 0.06) but the change in Ki67 was impeded even in those with high ER. Apoptotic index was reduced by 30% at 2 weeks in the **HER**-**2**-negative group. However, there were no statistically significant differences in apoptotic index between the groups. It is concluded that ER-positive/**HER**-**2** -positive primary breast carcinomas show an impeded antiproliferative response to endocrine therapy that nonetheless may vary between individual treatments. This together with high baseline proliferation is likely to translate to poor clinical response.

6/3,AB/24 (Item 24 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

12653732 21615583 PMID: 11748447
The role of **HER**-**2** oncoprotein in **drug**-sensitivity in breast cancer (Review).
Kim R; Tanabe K; Uchida Y; Osaki A; Toge T
Department of Surgical Oncology, Research Institute for Radiation Biology and Medicine, Hiroshima University, Hiroshima 734-8553, Japan.
Oncology reports (Greece) Jan-Feb 2002, 9 (1) p3-9, ISSN 1021-335X Journal Code: 9422756
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: In Process
Overexpression of human epidermal growth factor receptor-2 (**HER**-**2**) oncoprotein is an important prognostic factor associated with a poor prognosis in breast cancer. Although treatment with trastuzumab, an anti-**HER**-**2** antibody, increases **drug**-sensitivity in vitro and in vivo, the role of **HER**-**2** oncoprotein in **drug** -sensitivity is still uncertain. The present work discusses the clinical significance of the **HER**-**2** oncoprotein in **drug**-sensitivity in breast cancer based on previous clinical and basic results and reviews the current concept of **HER**-**2** oncoprotein in **drug** -sensitivity. Introduction of **HER**-**2** oncoprotein in vitro induces **resistance** to several anticancer drugs, including taxanes, cisplatin (CDDP) and 5-fluorouracil (5-FU) in breast cancer cells. The acquisition of **drug**-**resistance** by introduction of the **HER** -**2** gene, however, depends on the cell type, because transfection of the **HER**-**2** gene per se does not necessarily induce **resistance** to the same drugs in all types of breast cancer cells. In clinical studies, patients with **HER**-**2** overexpression responded better to an anthracycline-based regimen than patients with low **HER**-**2** expression, and their overall survival was also superior. In contrast, a correlation between the response to a cyclophosphamide + methotrexate + 5-FU regimen and overexpression of **HER**-**2** is not certain. Taxanes responsiveness in patients with **HER**-**2** oncoprotein overexpression was superior in patients with low **HER**-**2** expression. Treatment with trastuzumab increased **drug** -sensitivity to anthracyclines, CDDP, and taxanes, but not to 5-FU, in breast cancer cells. Although the mechanism(s) by which trastuzumab enhances **drug**-sensitivity is not fully understood, modulation of the signal transduction pathways leading to apoptosis, such as down-regulation of the anti-apoptotic protein, Bcl-2, might be an important target to

increase **drug**-sensitivity in breast cancer. **HER-2** overexpression can be a good indicator for the selection of aniticancer drugs, especially for anthracycline containing regimens. To modulate **HER-2** -targeting therapy, the mechanism(s) by which trastuzumab enhances **drug** -sensitivity requires elucidation at the molecular level, including determination of other factors that influence **drug** -sensitivity, leading to a more promising treatment for individual patients receiving combination therapy with trastuzumab and anticancer drugs for breast cancer.

6/3,AB/25 (Item 25 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

12643254 21600197 PMID: 11737891
Update on **HER-2** as a target for cancer therapy: Alternative strategies for targeting the epidermal growth factor system in cancer.
Gullick W J
Department of Biosciences, University of Kent at Canterbury, Canterbury, Kent, UK. W.J.Gullick@ukc.ac.uk
Breast cancer research : BCR (England) 2001, 3 (6) p390-4, ISSN 1465-5411 Journal Code: 100927353
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: In Process
The epidermal growth factor (EGF) family of ligands and receptors interact to influence cell division, differentiation and motility. Much evidence supports their importance in causing and sustaining cell transformation in model systems and in human cancer. The exact mechanism by which this is achieved varies in different tumour types and from case to case. The EGF system is a target for new types of targeted chemotherapy. The choice of strategy will depend on the mechanism involved, however, and several approaches are under development or evaluation in clinical trials. Each will have a different spectrum of side effects and the potential for development of **drug resistance**.

6/3,AB/26 (Item 26 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

12554968 21450617 PMID: 11566616
mTOR, a novel target in breast cancer: the effect of CCI-779, an mTOR inhibitor, in preclinical models of breast cancer.
Yu K; Toral-Barza L; Discafani C; Zhang W G; Skotnicki J; Frost P; Gibbons J J
Wyeth-Ayerst Research, Department of Oncology, 401 North Middletown Road, Pearl River, New York 10965, USA.
Endocrine-related cancer (England) Sep 2001, 8 (3) p249-58, ISSN 1351-0088 Journal Code: 9436481
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
The mammalian target of rapamycin (mTOR) is a central regulator of G1 cell cycle protein synthesis that precedes commitment to normal cellular replication. We have studied the effect of cell cycle inhibitor-779 (CCI-779), a rapamycin ester that inhibits mTOR function, on the proliferation of a panel of breast cancer cell lines. Six of eight lines studied were sensitive (IC(50)< or = 50 nM) and two lines were **resistant** (IC(50)>1.0 microM) to CCI-779. Sensitive lines were estrogen dependent (MCF-7, BT-474, T-47D), or lacked expression of the tumor suppressor PTEN (MDA-MB-468, BT-549), and/or overexpressed the **Her-2/neu** oncogene (SKBR-3, BT-474). **Resistant**

lines (MDA-MB-435, MDA-MB-231) shared none of these properties. CCI-779 (50 nM) inhibited mTOR function in both a sensitive and a **resistant** line. In nu/nu mouse xenografts, CCI-779 inhibited growth of MDA-MB-468 (sensitive) but not MDA-MB-435 **resistant** tumors. Treatment of sensitive lines with CCI-779 resulted in a decrease in D-type cyclin and c-myc levels and an increase in p27(kip-1) levels. There was good correlation between activation of the Akt pathway and sensitivity to CCI-779. Amplification of mTOR-regulated p70S6 kinase, which is downstream of Akt, may also have conferred CCI-779 sensitivity to MCF-7 cells. Taken together, the data suggest that mTOR may be a good target for breast cancer therapy, especially in tumors with Akt activation resulting from either growth factor dependency or loss of PTEN function.

6/3,AB/27 (Item 27 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

12554962 21450611 PMID: 11566610
Overexpression of **HER-2** as a **resistance** mechanism to hormonal therapy for breast cancer.
Dowsett M
Department of Biochemistry, Royal Marsden Hospital, London SW3 6JJ, UK. mitch@icr.ac.uk
Endocrine-related cancer (England) Sep 2001, 8 (3) p191-5, ISSN 1351-0088 Journal Code: 9436481
Document type: Journal Article; Review; Review, Tutorial
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
Hormonal therapy leads to improved survival in oestrogen receptor (ER) positive early breast cancer and long-term responses in advanced disease. However, **resistance** to such therapy is a serious clinical problem. This article considers the data for and against there being a significant role for the oncogene **HER-2** in such **resistance** . Transfection of **HER-2** into MCF-7 cells leads to **resistance** to tamoxifen but data differ in relation to the oestrogen dependence of such cells. A number of retrospective studies have been conducted of **HER-2** status in adjuvant trials of tamoxifen. Most of these also suggest a negative role but individually the studies do not have the statistical power to be conclusive. Recent studies in the neoadjuvant context have shown a significant antiproliferative effect of endocrine therapy in **HER-2** positive/ER positive tumours but this is much less than in **HER-2** negative/ER positive tumours. It is concluded that incomplete hormonal **resistance** results from co-expression of **HER-2** and ER and that this may differ between different hormonal agents.

6/3,AB/28 (Item 28 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

11361891 21443822 PMID: 11559718
Letrozole is more effective neoadjuvant endocrine therapy than tamoxifen for ErbB-1- and/or ErbB-2-positive, estrogen receptor-positive primary breast cancer: evidence from a phase III randomized trial.
Ellis M J; Coop A; Singh B; Mauriac L; Llombert-Cussac A; Janicke F; Miller W R; Evans D B; Dugan M; Brady C; Quebe-Fehling E; Borgs M
Duke University Breast Cancer Program, Duke University Comprehensive Cancer Center, Durham, NC 27710, USA. ellis053@mc.duke.edu
Journal of clinical oncology : official journal of the American Society of Clinical Oncology (United States) Sep 15 2001, 19 (18) p3808-16, ISSN 0732-183X Journal Code: 8309333
Comment in J Clin Oncol. 2001 Sep 15;19(18) 3795-7; Comment in PMID 11559715

Document type: Clinical Trial; Clinical Trial, Phase III; Journal Article ; Randomized Controlled Trial
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed

PURPOSE: Expression of ErbB-1 and ErbB-2 (epidermal growth factor receptor and HER2/**neu**) in breast cancer may cause tamoxifen **resistance** , but not all studies concur. Additionally, the relationship between ErbB-1 and ErbB-2 expression and response to selective aromatase inhibitors is unknown. A neoadjuvant study for primary breast cancer that randomized treatment between letrozole and tamoxifen provided a context within which these issues could be addressed prospectively. PATIENTS AND METHODS: Postmenopausal patients with estrogen- and/or progesterone receptor-positive (ER+ and/or PgR+) primary breast cancer ineligible for breast-conserving surgery were randomly assigned to 4 months of neoadjuvant letrozole 2.5 mg daily or tamoxifen 20 mg daily in a double-blinded study. Immunohistochemistry (IHC) for ER and PgR was conducted on pretreatment biopsies and assessed by the Allred score. ErbB-1 and ErbB-2 IHC were assessed by intensity and completeness of membranous staining according to published criteria. RESULTS: For study biopsy-confirmed ER+ and/or PgR+ cases that received letrozole, 60% responded and 48% underwent successful breast-conserving surgery. The response to tamoxifen was inferior (41%, P =.004), and fewer patients underwent breast conservation (36%, P =.036). Differences in response rates between letrozole and tamoxifen were most marked for tumors that were positive for ErbB-1 and/or ErbB-2 and ER (88% v 21%, P =.0004). CONCLUSION: ER+, ErbB-1+, and/or ErbB-2+ primary breast cancer responded well to letrozole, but responses to tamoxifen were infrequent. This suggests that ErbB-1 and ErbB-2 signaling through ER is ligand-dependent and that the growth-promoting effects of these receptor tyrosine kinases on ER+ breast cancer can be inhibited by potent estrogen deprivation therapy.

6/3,AB/29 (Item 29 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

11359506 21439119 PMID: 11555582
Circulating **HER**-2/erbB-2/c-**neu** (**HER-2**) extracellular domain as a prognostic factor in patients with metastatic breast cancer: Cancer and Leukemia Group B Study 8662.

Hayes D F; Yamauchi H; Broadwater G; Cirrincione C T; Rodrigue S P; Berry D A; Younger J; Panasci L L; Millard F; Duggan D B; Norton L; Henderson I C
Georgetown University Medical Center, Washington, DC 20007, USA. hayesdf@umich.edu

Clinical cancer research : an official journal of the American Association for Cancer Research (United States) Sep 2001, 7 (9) p2703-11, ISSN 1078-0432 Journal Code: 9502500
Contract/Grant No.: 60138; PHS; CA02599; CA; NCI; CA03927; CA; NCI; CA04326; CA; NCI; CA04457; CA; NCI; CA07968; CA; NCI; CA08025; CA; NCI; CA11028; CA; NCI; CA11789; CA; NCI; CA12046; CA; NCI; CA12449; CA; NCI; CA16450; CA; NCI; CA21060; CA; NCI; CA26806; CA; NCI; CA31809; CA; NCI; CA31946; CA; NCI; CA31983; CA; NCI; CA32291; CA; NCI; CA33601; CA; NCI; CA35406; CA; NCI; CA37135; CA; NCI; CA37447; CA; NCI; CA41287; CA; NCI; CA45374; CA; NCI; CA45389; CA; NCI; CA45400; CA; NCI; CA45418; CA; NCI; CA45564; CA; NCI; CA45808; CA; NCI; CA47545; CA; NCI; CA47555; CA; NCI; CA47559; CA; NCI; CA47577; CA; NCI; CA47642; CA; NCI; CA54697; CA; NCI; CA74811; CA; NCI; CA77298; CA; NCI; CA77406; CA; NCI; CA77440; CA; NCI; CA77597; CA; NCI; CA77651; CA; NCI; RO3CA53336; CA; NCI
Comment in Clin Cancer Res. 2001 Sep;7(9) 2601-4; Comment in PMID 11555568; Comment in Clin Cancer Res. 2001 Sep;7(9):2605-7; Comment in PMID 11555569
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM

Record type: Completed
PURPOSE: The **HER**-2/erbB-2/c-**neu** (**HER-2**) proto-oncogene is a M(r) 185,000 transmembrane tyrosine kinase that is amplified and/or overexpressed by 20-40% of breast cancers. **HER-2** has been associated with worse prognosis and **resistance** or sensitivity to specific treatment. We evaluated circulating levels of extracellular domain of **HER-2** (ECD/**HER-2**) in metastatic breast cancer patients and investigated the prognostic and predictive significance of circulating **HER-2** levels regarding endocrine therapy or chemotherapy. EXPERIMENTAL DESIGN: Plasma samples from 242 patients were assayed for circulating ECD/**HER-2** levels, using a sandwich enzyme immunoassay. ECD/**HER-2** was correlated with clinical data gathered from these patients while they were participating in prospective Cancer and Leukemia Group B (CALGB) therapeutic protocols for metastatic breast cancer. RESULTS: Eighty-nine (37%) of 242 patients had elevated ECD/**HER-2** levels (> or =10.5 ng/ml). ECD/**HER-2** was significantly associated with tumor burden, progesterone receptor levels, and presence of visceral metastases. Patients with elevated pretreatment levels had a significantly shorter OS but not time-to-progression than did those with ECD/**HER-2** levels <10.5 ng/ml in univariate analysis. In univariate but not multivariate subset analyses, among patients treated with endocrine therapy (megestrol acetate), elevated initial ECD/**HER-2** was associated with worse OS compared with nonelevated patients. However, among patients treated with chemotherapy (mainly anthracycline-containing regimens), OS did not differ significantly. Rates of response to either endocrine therapy or chemotherapy were similar for patients with elevated and nonelevated ECD/**HER-2** levels. CONCLUSIONS: ECD/**HER-2** levels are elevated in 35-40% of patients with metastatic breast cancer. Elevated ECD/**HER-2** levels are associated with a poorer prognosis in these patients. However, no predictive role for ECD/**HER-2** was identified, either for endocrine therapy or for anthracycline-based chemotherapy in the metastatic setting.

6/3,AB/30 (Item 30 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

11348988 21415892 PMID: 11524552
Breast cancer.
Kuter I
Massachusetts General Hospital, Boston, Massachusetts 02114, USA. kuter.irene@mgh.harvard.edu
oncologist (United States) 2001, 6 (4) p338-46, ISSN 1083-7159 Journal Code: 9607837
Document type: Journal Article; Review; Review, Tutorial
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
Several interesting aspects of breast cancer were covered at this year's American Society of Clinical Oncology meeting. Sentinel lymph node (SN) mapping is now in widespread use, in concert with the general trend toward trying to decrease the morbidity of breast cancer surgery. With every advance, however, comes new challenges, and there was a timely presentation from Giuliano's group addressing the controversial issue of how to interpret the presence of cells in the SN seen only with keratin stains but not by routine hematoxylin and eosin stains. Two abstracts addressed the issue of whether for certain women with invasive breast cancer radiation therapy could be omitted after lumpectomy. Another interesting topic related to hormonal issues in the adjuvant treatment of premenopausal women. An analysis from the ZIPP-TRIAL reported on bone marrow density studies in young women given two years of ovarian suppression in the adjuvant setting: it seems that the loss of bone density may be reversible and, more interestingly, may be prevented with concurrent tamoxifen. Two

other presentations looked at the prognostic significance of **drug** -induced amenorrhea in young women treated with adjuvant chemotherapy and at the efficacy of ovarian suppression during chemotherapy in preserving fertility. In an unpublicized presentation, Mary-Claire King presented very interesting results from the National Surgical Adjuvant Breast and Bowel Project Breast Cancer Prevention Trial suggesting that tamoxifen may be an effective chemopreventive **drug** for women with BRCA2, but not BRCA1, mutations. Two important presentations re-analyzed the outcome of the pivotal trials using Herceptin to treat metastatic breast cancer and nicely show that FISH analysis of **HER-2** overexpression is a more accurate indicator of response to Herceptin than immunohistochemical staining. Finally, there were two interesting presentations related to tamoxifen **resistance** which may be relevant clinically, pertaining to subsequent raloxifene use and the interaction of the estrogen receptor and EGF receptor pathways, respectively.

6/3,AB/31 (Item 31 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

11340502 21398738 PMID: 11506816

Mechanism of up-regulated gap junctional intercellular communication during chemoprevention and chemotherapy of cancer.

Trosko J E; Chang C C

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Mutation research (Netherlands) Sep 1 2001, 480-481 p219-29, ISSN 0027-5107 Journal Code: 0400763

Document type: Journal Article; Review; Review, Tutorial

Languages: ENGLISH

Main Citation Owner: NLM

Record type: Completed

To develop a strategy for efficacious intervention in order to prevent or treat various cancers, one must understand the basic mechanism(s) by which various anticancer dietary factors prevent or reverse the tumor promotion or progression phases. Carcinogenesis is a multistage, multimechanism process, involving the irreversible alteration of a stem cell (the "initiation" phase), followed by the clonal proliferation of the initiated stem cell (the "promotion" phase), from which the acquisition of the invasive and metastatic phenotypes are generated (the "progression" phase). While intervention to prevent or treat cancer could occur at each step, the objective of this presentation will focus on the rate limiting step, the promotion phase.Gap junctional intercellular communication (GJIC) has been hypothesized to regulate growth control, differentiation and apoptosis. Most normal, contact-inhibited cells have functional GJIC, while most, if not all, tumor cells have dysfunctional homologous or heterologous GJIC. Cancer cells are characterized by the lack of growth control, by the inability to terminally differentiate and by **resistance** to apoptosis. Chemical tumor promoters (phorbol esters, DDT, phenobarbital, unsaturated fatty acids, saccharin, etc.) inhibit GJIC in a reversible fashion and at doses above particular chemical thresholds. Various oncogenes (e.g. ras, raf, **neu**, src, mos) down-regulate GJIC while several tumor suppressor genes can up-regulate GJIC. Antitumor promoters (retinoids, carotenoids, green tea components) and antioncogene drugs (i.e. lovastatin) can up-regulate GJIC. Transfection of gap junction genes ("connexins") into GJIC-deficient tumor cells can restore GJIC, growth control and reduce tumorigenicity. On the other hand, antisense gap junction genes can convert the phenotype of a non-tumorigenic cell to that of a tumorigenic one. Recently, a specific connexin knockout mouse was shown to have a higher frequency of spontaneous and induced liver cancers.Evidence from these studies clearly suggests that dietary factors can modulate GJIC by inducing various signal transducing systems. The modulation can either down-regulate

GJIC and lead to tumor promotion or it can up-regulate GJIC and lead to suppression of the initiated cells. Multiple mechanisms of up- or down-regulation of GJIC exist, as well as multiple types of pre-malignant and malignant tumor cells that are unable able to have functional GJIC. GJIC can be down-regulated by mutations and by epigenetic means. Alteration of gene expression at the transcriptional, translational or post-translational levels would require specific dietary prevention or treatment of cancer. In conclusion, if dietary prevention or treatment of cancer is to occur, it must ameliorate the growth-stimulatory effects, above threshold levels, of chemicals, growth factors or hormones, that trigger various mitogenic/antiapoptotic signal transducing systems that block GJIC.

6/3,AB/32 (Item 32 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

11336771 21396531 PMID: 11481456
Ethanol hypersensitivity and olfactory discrimination defect in mice lacking a homolog of Drosophila neuralized.
Ruan Y; Tecott L; Jiang M M; Jan L Y; Jan Y N
Departments of Physiology and Biochemistry, Howard Hughes Medical Institute, University of California, San Francisco 94143, USA.
Proceedings of the National Academy of Sciences of the United States of America (United States) Aug 14 2001, 98 (17) p9907-12, ISSN 0027-8424 Journal Code: 7505876
Contract/Grant No.: K02 MH01949; MH; NIMH
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
Neurogenic genes in the Notch receptor-mediated signaling pathway play important roles in neuronal cell fate specification as well as neuronal differentiation. The Drosophila neuralized gene is one of the neurogenic genes. We have cloned a mouse homolog of Drosophila neuralized, m-neu1, and found that the m-neu1 transcript is expressed in differentiated neurons. Mice deficient for m-neu1 are viable and morphologically normal, but exhibit specific defects in olfactory discrimination and hypersensitivity to ethanol. These findings reveal an essential role of m-neu1 in ensuring proper processing of certain information in the adult brain.

6/3,AB/33 (Item 33 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

11332742 21387650 PMID: 11496337
Pharmacokinetic and biochemical analysis in the treatment of weekly paclitaxel in relapsed breast cancer.
Kim R; Osaki A; Toge T
Department of Surgical Oncology, Research Institute for Radiation Biology and Medicine, Hiroshima University, Hiroshima, Japan. rkim@ipc.hiroshima-u.ac.jp
Oncology reports (Greece) Sep-Oct 2001, 8 (5) p1171-6, ISSN 1021-335X Journal Code: 9422756
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
The mechanism(s) by which weekly paclitaxel exerted more therapeutic efficacy than the triweekly schedule in relapsed breast cancer is still unclear. To assess the rationale in therapeutic efficacy of weekly paclitaxel in relapsed breast cancer, pharmacokinetic and biochemical analyses were examined in terms of the mean peak plasma concentration at 0 min (Cmax), 30 min, and 24 h after finishing the infusion, and the

extracellular domain of **HER-2** in response to the treatment with paclitaxel. Twenty-five patients treated with weekly 1 h infusion of paclitaxel in the dose range from 40 mg/m(2) to 80 mg/m(2) were studied. Eleven patients responded to the treatment including 4 cases of complete response (CR) and 7 cases of partial response (PR), while 14 patients did not respond including 12 cases of no change (NC) and 2 cases of progressive disease (PD). The plasma concentration of paclitaxel and extracellular domain of **HER-2** in the patients were measured by high-pressure liquid chromatography and enzyme immunoassay, respectively. The peak concentration (Cmax) and the other peaks at 30 min and 24 h in 10 patients including 3 cases of 40 mg/m(2), 3 cases of 60 mg/m(2) and 4 cases of 80 mg/m(2) in the weekly paclitaxel were compared in proportion to the increase of dose escalation, and compared to their tumor response. Further, the plasma levels of extracellular domain of **HER-2** in 17 patients treated with the weekly paclitaxel were measured, and also compared to their tumor response. The mean Cmax treated with 40 mg/m(2), 60 mg/m(2) and 80 mg/m(2) in the weekly paclitaxel was 1.94, 2.18 and 1.54 microM, respectively. The dose escalation of paclitaxel and the dose intensity were not correlated with the increase of plasma concentration of paclitaxel nor with the tumor response. In contrast, the plasma level of extracellular domain of **HER-2** in responders was higher than that of non-responders in the weekly paclitaxel regimen(p=0.0512, Mann-Whitney's U-test). These results suggest that tumor response to the weekly 1 h infusion of paclitaxel was not associated with the plasma concentration and the dose intensity, rather the plasma level of extracellular domain of **HER-2** protein may be a predictor of tumor response in the treatment of weekly paclitaxel in relapsed breast cancer.

6/3,AB/34 (Item 34 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

11316353 21371434 PMID: 11478139
[Endocrine therapy for advanced or recurrent breast cancer]
Sonoo H; Kurebayashi J
Department of Breast and Thyroid Surgery, Kawasaki Medical School, 577 Matsushima, Kurashiki 701-0192, Japan.
Gan to kagaku ryoho. Cancer & chemotherapy (Japan) Jul 2001, 28 (7) p909-16, ISSN 0385-0684 Journal Code: 7810034
Document type: Journal Article; Review; Review, Tutorial ; English Abstract
Languages: JAPANESE
Main Citation Owner: NLM
Record type: Completed

Endocrine therapy of advanced or recurrent breast cancer was described. The presence of ER or PgR in primary breast tumors is the best-established marker for response to endocrine therapy. However, ER-positive breast tumors overexpressing EGF-R and/or **HER-2** (Erb B2) are **resistant** to endocrine therapy. Recently it was suggested that an elevated level of the circulating extracellular domain of **HER-2** could be a predictor for poor response to endocrine therapy. LH-RH agonist is used as a first-line therapy for premenopausal patients. And LH-RH agonist plus tamoxifen (TAM) has shown a higher response rate and more prolonged survival than LH-RH agonist or TAM alone. As two new aromatase inhibitors, anastrozole (ANA) and letrozole, have shown an equal or higher response rate and a prolonged time to progression than TAM as a first-line therapy, these could be used as a first-line therapy instead of TAM. In a cross-over trial of ANA and TAM, the response rate of ANA after TAM failure was equal to that of TAM after ANA failure. As these drugs showed an equal or higher response rate and longer survival than progestin in TAM **resistant** cases, these drugs could also used as a second-line therapy. In addition, the trend of recent studies regarding the mechanisms of hormone **resistance** is also described.

6/3,AB/35 (Item 35 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

11287928 21322754 PMID: 11429595
Specific protection against breast cancers by cyclin D1 ablation.
Yu Q; Geng Y; Sicinski P
Department of Cancer Biology, Dana-Farber Cancer Institute, Harvard Medical School, Boston, Massachusetts 02115, USA.
Nature (England) Jun 28 2001, 411 (6841) p1017-21, ISSN 0028-0836
Journal Code: 0410462
Comment in Nature. 2001 Jun 28;411(6841) 1001-2; Comment in PMID 11429580
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
Breast cancer is the most common malignancy among women. Most of these cancers overexpress cyclin D1, a component of the core cell-cycle machinery. We previously generated mice lacking cyclin D1 using gene targeting. Here we report that these cyclin D1-deficient mice are **resistant** to breast cancers induced by the **neu** and ras oncogenes. However, animals lacking cyclin D1 remain fully sensitive to other oncogenic pathways of the mammary epithelium, such as those driven by c-myc or Wnt-1. Our analyses revealed that, in mammary epithelial cells, the **Neu** -Ras pathway is connected to the cell-cycle machinery by cyclin D1, explaining the absolute dependency on cyclin D1 for malignant transformation in this tissue. Our results suggest that an anti-cyclin D1 therapy might be highly specific in treating human breast cancers with activated **Neu**-Ras pathways.

6/3,AB/36 (Item 36 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

11286269 21327651 PMID: 11433610
Measurement of **HER-2/neu** in breast cancer: which methodologic approach?]
Determinazione di **HER-2/neu** nel carcinoma mammario: quale approccio metodologico?
Orvieto E; Dei Tos A P
Servizio di Anatomia Patologica e Citodiagnostica, Ospedale Civile di Treviso, Piazza Ospedale 1, I-31100 Treviso.
Pathologica (Italy) Jun 2001, 93 (3) p183-8, ISSN 0031-2983
Journal Code: 0401123
Document type: Editorial ; English Abstract
Languages: ITALIAN
Main Citation Owner: NLM
Record type: Completed
HER-2/neu (c-erbB2) is overexpressed or amplified in 15%-35% of breast cancers. **HER-2** testing has become of paramount importance as it represents a key therapeutic, prognostic and predictive parameter. **HER-2** is associated with ER/PgR negativity, high histologic grade, high proliferative index, and increased number of metastatic lymph nodes. In N+ patients, **HER-2** represents a negative prognostic factor. **HER-2** also represents a predictive factor. In fact, **HER-2**+ patients appear to be **resistant** to the CMF regimen and comparatively more sensitive to anthracyclins such as Herceptin. **HER-2** testing is currently performed utilizing two main methods: gene amplification is usually determined by fluorescence in situ hybridization (FISH), whereas protein overexpression is determined by immunohistochemistry (IHC). The comparison between FISH and IHC assays demonstrates a considerably high degree of concordance (around 90%). When dealing with cases scored as 3+ (according

to the FDA licensed scoring method), such a concordance approaches 100%. In consideration of greater technical simplicity as well as of cost-effectiveness, IHC represents the ideal screening method for **HER-2** testing. FISH analysis remains valid for **HER-2** evaluation in those cases in which IHC fails to provide unequivocal data.

6/3,AB/37 (Item 37 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

11271400 21303166 PMID: 11410482
Induction of topoisomerase II activity after ErbB2 activation is associated with a differential response to breast cancer chemotherapy.
Harris L N; Yang L; Liotcheva V; Pauli S; Iglehart J D; Colvin O M; Hsieh T S
Adult Oncology, Dana-Farber Cancer Institute, Boston, Massachusetts 02115, USA.
Clinical cancer research : an official journal of the American Association for Cancer Research (United States) Jun 2001, 7 (6) p1497-504, ISSN 1078-0432 Journal Code: 9502500
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
ErbB2 (**HER-2**) gene amplification and overexpression have been shown to predict a better outcome with doxorubicin-based chemotherapy as opposed to alkylator-based chemotherapy in early stage breast cancer. To understand the mechanism of differential response to these two regimens, we have evaluated the effect of signaling through the ErbB2 receptor on downstream enzymes that may affect **drug** response, using two different models. The first system employs breast cancer cells that have high levels of endogenous ErbB2 by gene amplification (BT-474 and SKBR3 cells). The second system allows us to isolate the effect of ErbB2 receptor-mediated intracellular signaling using an epidermal growth factor receptor-ErbB2 chimeric receptor activated by epidermal growth factor. Our experiments show that the cytotoxicity of doxorubicin is inhibited in ErbB2+ breast cancer cells by the anti-ErbB2 antibody, Herceptin. This is accompanied by a decrease in topoisomerase (topo) IIalpha protein and activity, suggesting that this is the mechanism of change in doxorubicin response. In addition, a 10-100-fold (1-2 log) decrease in the LD(50) of doxorubicin is seen after ErbB2 activation using the chimeric receptor model. Furthermore, we see a 100-fold decrease in the LD(50) of etoposide, another topo II inhibitor. This increase in doxorubicin sensitivity is associated with a 4.5-fold increase in the amount of topo IIalpha protein and an increase in topo II activity as measured by DNA decatenating and unknotting activities, as well as cleavable complex formation. In contradistinction to doxorubicin, we have observed an increased **resistance** to cyclophosphamide chemotherapy after chimeric receptor activation. We propose that the differential benefit seen with doxorubicin- versus alkylator-based chemotherapy in ErbB2+ breast cancer is due, in some cases, to ErbB2-mediated topo IIalpha activation. These data also suggest hypotheses for the optimal sequencing of Herceptin and chemotherapy agents in ErbB2+ breast cancer.

6/3,AB/38 (Item 38 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

11264784 21292569 PMID: 11399867
Increased sensitivity to cisplatin in gastric cancer by antisense inhibition of the **her-2/neu** (c-erbB-2) gene.
Funato T; Kozawa K; Fujimaki S; Miura T; Kaku M
Division of Molecular Diagnostics, Department of Clinical Medicine, Tohoku University School of Medicine, Sendai, Japan.

tfunato@mail.cc.tohoku.ac.jp
Chemotherapy (Switzerland) Jul-Aug 2001, 47 (4) p297-303, ISSN 0009-3157 Journal Code: 0144731
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
BACKGROUND: The c-erbB-2 oncogene encodes a transmembrane tyrosine kinase receptor and its abnormal expression may be related to the prognosis of gastric cancer. Gastric cancer is relatively **resistant** to various drugs, including cisplatin. Cisplatin is widely used in cancer chemotherapy, but the mechanisms of **drug resistance** are not yet known. METHODS: We used the human gastric cancer cell lines MKN-7 and KATO-III, which express the c-erbB-2 oncogene, as a model for relative **resistance** to cisplatin. We investigated whether inhibition with antisense oligonucleotides against c-erbB-2 increased the sensitivity of MKN-7 and KATO-III cells to cisplatin. Results: Antisense oligonucleotides for c-erbB-2 inhibited the expression of c-erbB-2 mRNA and protein and increased sensitivity to cisplatin, but not to other drugs, in MKN-7 and KATO-III cells. Cell growth was also inhibited by c-erbB-2 antisense oligonucleotides but not sense oligonucleotides. CONCLUSION: These findings indicate that c-erbB-2 expression in gastric cancer is one of the factors related to cisplatin sensitivity, and that anti-c-erbB-2 antisense oligonucleotides induced increased sensitivity to cisplatin.

6/3,AB/39 (Item 39 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

11250335 21278284 PMID: 11384104
Decrease in **drug** accumulation and in tumour aggressiveness marker expression in a fenretinide-induced **resistant** ovarian tumour cell line.
Appierto V; Cavadini E; Pergolizzi R; Cleris L; Lotan R; Canevari S; Formelli F
Department of Experimental Oncology, Istituto Nazionale Tumori, Milan, 20133, Italy.
British journal of cancer (Scotland) Jun 1 2001, 84 (11) p1528-34, ISSN 0007-0920 Journal Code: 0370635
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
We investigated whether the efficacy of fenretinide (HPR) against ovarian tumours may be limited by induction of **resistance**. The human ovarian carcinoma cell line A2780, which is sensitive to a pharmacologically achievable HPR concentration (IC(50)= 1 microM), became 10-fold more **resistant** after exposure to increasing HPR concentrations. The cells (A2780/HPR) did not show cross-**resistance** to the synthetic retinoid 6-[3-adamantyl-4-hydroxyphenyl]-2-naphthalene carboxylic acid (CD437) and were not sensitive, similarly to the parent line, to all-trans-retinoic acid, 13-cis-retinoic acid or N-(4-methoxyphenyl)retinamide. A2780/HPR cells showed, compared to parental cells, a 3-fold reduction in colony-forming ability in agar. The development of HPR **resistance** was associated with a marked increase in retinoic acid receptor beta (RARbeta) mRNA and protein levels, which decreased, together with **drug resistance**, after **drug** removal. The expression of cell surface molecules associated with tumour progression including **HER-2**, laminin receptor and beta1 integrin was markedly reduced. The increase in the levels of reactive oxygen species is not involved in HPR-**resistance** because it was similar in parental and **resistant** cells. Conversely differences in pharmacokinetics may account for **resistance** because, in A2780/HPR cells, intracellular peak **drug** levels were 2 times lower than in A2780 cells and an as yet unidentified

polar metabolite was present. These data suggest that acquired **resistance** to HPR is associated with changes in marker expression, suggestive of a more differentiated status and may be explained, at least in part, by reduced **drug** accumulation and increased metabolism.
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6/3,AB/40 (Item 40 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

11232159 21253143 PMID: 11353797
Pharmacological separation of the expression of tissue transglutaminase and apoptosis after chemotherapeutic treatment of HepG2 cells.
Uray I P; Davies P J; Fesus L
Department of Biochemistry and Molecular Biology, University of Debrecen, Medical and Health Science Center, Faculty of Medicine, H-4012 Debrecen, Hungary.
Molecular pharmacology (United States) Jun 2001, 59 (6) p1388-94, ISSN 0026-895X Journal Code: 0035623
Contract/Grant No.: CA76088; CA; NCI
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
Chemotherapeutic drugs are known to eliminate cancer cells by inducing apoptosis. Tissue transglutaminase (tTG), a frequent player in apoptotic processes, is markedly induced in **drug-resistant** cancer cells.
To better understand the action of apoptosis-inducing drugs, our study elucidates changes in the expression of tTG in the early phase of cell death, before the downstream events of apoptosis. We demonstrate that HepG2 cells uniformly induce both tTG mRNA and enzyme activity upon treatment with cisplatin, doxorubicin, and bleomycin, chemotherapeutic agents with different modes of action. The expression of fas ligand, caspase3 and baxalpha changes differentially or remain unaffected. tTG expression did not change significantly after administration of either the peroxisome proliferator activated receptor-alpha agonist WY14643 or the retinoid X receptor-specific analog LG 100268. However, both compounds blocked **drug** -induced tTG induction without affecting the extent of cell death. The pleiotropic cytokine interleukin-6 effectively rescued hepatoma cells from apoptosis while tTG induction still took place, along with the induction of antiapoptotic transcripts bcl-x(L), gp130, and her2/**neu**.
These results suggest that the induction of tTG, although present in **drug** -induced apoptosis, is pharmacologically dissociable from the early, initiating events of apoptosis. Blocking the induction of tTG during **drug** -induced cell death may alleviate limiting side effects of anticancer agents, including fibrosis and neuropathies.

6/3,AB/41 (Item 41 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

11208188 21229669 PMID: 11330951
The clinical utility of liposomal doxorubicin in recurrent ovarian cancer.
Campos S M; Penson R T; Mays A R; Berkowitz R S; Fuller A F; Goodman A; Matulonis U A; Muzikansky A; Seiden M V
Dana Farber Cancer Institute and the Brigham and Women's Hospital, Boston, MA 02115, USA.
Gynecologic oncology (United States) May 2001, 81 (2) p206-12, ISSN 0090-8258 Journal Code: 0365304
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed

OBJECTIVES: The aim of this study was to determine the efficacy and toxicity of single agent off-protocol, liposomal doxorubicin (Doxil Alza), in consecutive patients with recurrent ovarian cancer and to investigate the influence of **HER-2/neu** expression on response to liposomal doxorubicin. PATIENTS AND METHODS: Retrospective analysis of 72 consecutive patients treated, typically with liposomal doxorubicin 40 mg/m(2) q28 days between January 1997 and December 1998. Results. Twenty-nine patients (40%) had platinum- and taxane-**resistant** tumors. Nineteen patients (27%) responded with clinical or radiological evidence of response with reduction in CA-125 of >50%. One complete response (CR) and 7 partial responses (PRs) occurred in platinum- and taxane-**resistant** patients (radiological response (RR) 29%) and 8 PRs occurred in patients with visceral metastases (RR 28%). Time to progression was 5.3 (2.1-12.1) months. Only 7 dose delays (3%) and 20 dose reductions (8%) were necessary in 265 cycles of treatment. Hematological toxicity was generally mild with grade (Gr) > or =III neutropenia in 1 (2%), Gr > or =III thrombocytopenia in 1 (1%), and Gr > or =III anemia in 8 patients (11%). One patient (1%) was admitted with fever and neutropenia. Other toxicity was minimal with Gr > or =III mucositis occurring in 3 patients (4%). Gr > or =III cutaneous toxicity was seen in 6 patients (8%). Three patients (4%) had a >10% fall in ejection fraction but there was no unequivocal clinical heart failure. CONCLUSIONS: The data suggest that liposomal doxorubicin is an active **drug** in both taxane- and platinum-sensitive and **resistant** recurrent ovarian cancer. Liposomal doxorubicin is associated with tolerable toxicity and is particularly well tolerated in patients with multiple prior lines of treatment. Copyright 2001 Academic Press.

6/3,AB/42 (Item 42 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

11187746 21205839 PMID: 11309298

E1A sensitizes HER2/**neu** -overexpressing Ewing's sarcoma cells to topoisomerase II-targeting anticancer drugs.

Zhou Z; Jia S F; Hung M C; Kleinerman E S

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Cancer research (United States) Apr 15 2001, 61 (8) p3394-8, ISSN 0008-5472 Journal Code: 2984705R

Contract/Grant No.: CA16672; CA; NCI; CA82606; CA; NCI

Document type: Journal Article

Languages: ENGLISH

Main Citation Owner: NLM

Record type: Completed

Overexpression of the HER2/**neu** oncogene is associated with tumorigenicity and **drug resistance** in many types of cancer. Three different human Ewing's sarcoma cell lines (TC71, RD, and A4573) were found to express high levels of the HER2/**neu** protein. Transduction of TC71 cells with the E1A gene using an adenoviral vector (Ad-E1A) down-regulated HER2/**neu** overexpression in those cells and increased cytostasis. E1A-induced apoptosis was demonstrated by both flow cytometric analysis and Western blot analysis using a poly(ADP-ribose) polymerase antibody. After transduction of the E1A gene into these cells, the sensitivity of these cells to VP-16 (etoposide) was enhanced 18-fold and to Adriamycin 5-fold. However, no change was seen in cisplatin sensitivity. E1A also significantly increased topoisomerase IIalpha protein expression, indicating that the up-regulation of topoisomerase IIalpha may be one of the mechanisms by which E1A enhanced the sensitivity to topoisomerase II-targeting anticancer drugs, such as VP-16 and Adriamycin, but not cisplatin. In summary, these studies demonstrated that Ad-E1A can down-regulate HER2/**neu** overexpression and up-regulate topoisomerase IIalpha expression in human Ewing's sarcoma cells, increasing their apoptosis rate and enhancing their sensitivity to VP-16 and ADRIAMYCIN:

6/3,AB/43 (Item 43 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

11187303 21204024 PMID: 11306725
Chemotherapy of metastatic breast cancer: what to expect in 2001 and beyond.
Esteva F J; Valero V; Pusztai L; Boehnke-Michaud L; Buzdar A U; Hortobagyi G N
Department of Breast Medical Oncology, The University of Texas M.D. Anderson Cancer Center, 1515 Holcombe Blvd., Box 56, Houston, TX 77030, USA. festeva@mdanderson.org
oncologist (United States) 2001, 6 (2) p133-46, ISSN 1083-7159
Journal Code: 9607837
Contract/Grant No.: K23-CA82119; CA; NCI
Document type: Journal Article; Review; Review, Academic
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
Chemotherapy plays an important role in the management of metastatic breast cancer. The anthracyclines (doxorubicin, epirubicin) and the taxanes (paclitaxel, docetaxel) are considered the most active agents for patients with advanced breast cancer. Traditionally, the anthracyclines have been used in combination with cyclophosphamide and 5-fluorouracil (FAC, FEC). The taxanes have single-agent activity similar to older combination chemotherapy treatments. There is great interest in developing anthracycline/taxane combinations. Capecitabine is indicated for patients who progress after anthracycline and taxane therapy. Vinorelbine and gemcitabine have activity in patients with metastatic breast cancer and are commonly used as third- and fourth-line palliative therapy. The role of high-dose chemotherapy is not well-defined and remains experimental. Novel cytotoxic therapy strategies include the development of anthracycline, taxane, and oral fluoropyrimidine analogues; antifolates; topoisomerase I inhibitors, and multidrug **resistance** inhibitors. A better understanding of the biology of breast cancer is providing novel treatment approaches. Oncogenes and tumor-supressor genes are emerging as important targets for therapy. Trastuzumab, a monoclonal antibody directed against the **Her-2/neu** protein, has been shown to prolong survival in patients with metastatic breast cancer. Other novel biologic therapies interfere with signal transduction pathways and angiogenesis. The challenge for the next decade will be to integrate these promising agents in the management of metastatic and primary breast cancer.

6/3,AB/44 (Item 44 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

11170966 21201416 PMID: 11304726
Antitumor effect of an HER2-specific antibody-toxin fusion protein on human prostate cancer cells.
Wang L; Liu B; Schmidt M; Lu Y; Wels W; Fan Z
Department of Experimental Therapeutics, The University of Texas M.D. Anderson Cancer Center, Houston, Texas, USA.
Prostate (United States) Apr 2001, 47 (1) p21-8, ISSN 0270-4137
Journal Code: 8101368
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
BACKGROUND: HER2/**neu** has been implicated in the oncogenesis of human prostate cancer. Clinical studies have suggested that overexpression of HER2 may be one of the indicators of poor prognosis in prostate cancer patients. METHODS: We used Western blot analysis to examine the expression

of HER2 in a panel of established human prostate cancer cell lines and used an MTT assay to evaluate the cytotoxicity on these cells of a recombinant fusion protein consisting of an HER2-specific single-chain antibody and the Pseudomonas exotoxin A, scFv(FRP5)-ETA. RESULTS: LNCaP cells express high levels of HER2 protein. Exposure of LNCaP cells to scFv(FRP5)-ETA caused remarkable cell death. In contrast, PC3M cells, which express an undetectable level of HER2 protein, were **resistant** to scFv(FRP5)-ETA-induced cytotoxicity. MDA PCa 2a, MDA PCa 2b, and DU145 cells express low-to-medium levels of HER2 protein and showed an HER2 level-dependent response to scFv(FRP5)-ETA-induced cytotoxicity. The scFv(FRP5)-ETA-induced cytotoxicity of LNCaP cells could be inhibited by an anti-HER2 monoclonal antibody (mAb), which downregulated the levels of HER2 protein, indicating the specificity of scFv(FRP5)-ETA in inducing cytotoxicity in LNCaP cells. Using an apoptosis ELISA, we demonstrated that scFv(FRP5)-ETA induced apoptosis in LNCaP cells. The apoptosis was inhibited by the presence of dihydrotestosterone (DHT) in culture medium. Exposure of LNCaP cells to scFv(FRP5)-ETA caused reduction in the level of the prostate-specific antigen (PSA). CONCLUSIONS: Our data suggest that scFv(FRP5)-ETA might be a useful agent for the treatment of human prostate cancer cells with high levels of HER2 expression.

6/3,AB/45 (Item 45 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

11151951 21174939 PMID: 11280726
Geldanamycin and its analogue 17-allylamino-17-demethoxygeldanamycin lowers Bcr-Abl levels and induces apoptosis and differentiation of Bcr-Abl-positive human leukemic blasts.
Nimmanapalli R; O'Bryan E; Bhalla K
Interdisciplinary Oncology Program, Moffitt Cancer Center, University of South Florida, Tampa 33612, USA.
Cancer research (United States) Mar 1 2001, 61 (5) p1799-804, ISSN 0008-5472 Journal Code: 2984705R
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
HL-60/Bcr-Abl cells, with ectopic expression of p185 Bcr-Abl tyrosine kinase (TK), and K562 cells, with endogenous expression of p210 Bcr-Abl TK, display a high degree of **resistance** against antileukemic **drug** -induced apoptosis (G. Fang et al., Blood, 96: 2246-2256, 2000). Present studies demonstrate that treatment with ansamycin antibiotic geldanamycin (GA), or its less toxic analogue 17-allylamino-17-demethoxygeldanamycin (17-AAG), induces cytosolic accumulation of cytochrome c and cleavage and activities of caspase-9 and caspase-3, triggering apoptosis of HL-60/Bcr-Abl and K562 cells. GA or 17-AAG down-regulated intracellular Bcr-Abl and c-Raf protein levels, as well as reduced Akt kinase activity. Similar to Raf-1, v-Src, and **Her-2-neu**, Bcr-Abl TK has chaperone association with heat shock protein 90 (Hsp90). By binding and inhibiting Hsp90, GA or 17-AAG treatment shifted the binding of Bcr-Abl from Hsp90 to Hsp70 and induced the proteasomal degradation of Bcr-Abl, because cotreatment with proteasome inhibitor PSC341 reduced both GA (or 17-AAG)-mediated down-regulation of Bcr-Abl levels and inhibited apoptosis of HL-60/Bcr-Abl and K562 cells. These data establish the in vitro activity of GA and 17-AAG against Bcr-Abl-positive leukemic cells and support the in vivo investigation of 17-AAG against Bcr-Abl-positive leukemias.

6/3,AB/46 (Item 46 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

11143880 21150318 PMID: 11250999
Comparison of methods of measuring **HER-2** in metastatic breast

cancer patients treated with high-dose chemotherapy.
Harris L N; Liotcheva V; Broadwater G; Ramirez M J; Maimonis P; Anderson S; Everett T; Harpole D; Moore M B; Berry D A; Rizzeri D; Vredenburgh J J; Bentley R C
Dana-Farber Cancer Institute, Boston, MA 02115, USA.
Journal of clinical oncology : official journal of the American Society of Clinical Oncology (United States) Mar 15 2001, 19 (6) p1698-706, ISSN 0732-183X Journal Code: 8309333
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
PURPOSE: **HER-2** is overexpressed in 20% to 30% of human breast cancer and is associated with poor outcome. Studies suggest an association between **HER-2** overexpression and **resistance** to alkylating agents. To further evaluate this relationship, we assessed the interaction of **HER-2**, measured by different methods, and outcome after dose intensification with alkylating agents in metastatic breast cancer. PATIENTS AND METHODS: From 1988 to 1995 at Duke University, 425 patients with metastatic breast cancer were enrolled in a study of high-dose alkylating agents (HDC) with autologous cellular support after doxorubicin-based therapy (AFM). **HER-2** was measured in serum for shed extracellular domain (ECD) and in tissue by immunohistochemistry (IHC) and fluorescent in situ hybridization (FISH). RESULTS: **HER-2** ECD was positive in 29% (19 of 65) of patients pre-AFM and in 11.7% (34 of 290) pre-HDC. Higher pre-AFM and higher pre-HDC **HER-2** ECD predicted worse overall survival (P =.045 and P =.0096, respectively). **HER-2** overexpression by IHC and FISH showed no correlation with worse disease-free survival or overall survival. FISH and ECD were highly specific for IHC (97.3% and 97.7% respectively). However, ECD had a low sensitivity for IHC-only 22% of patients with **HER-2** in the primary tumor shed ECD into the serum. CONCLUSION: These data suggest that the method of measuring **HER-2** is important in predicting clinical outcome. HER2 ECD may identify a poor prognosis subgroup of **HER-2** -positive tumors. Lack of association of HER2 by IHC/FISH with worse outcome suggests that therapy with AFM and/or HDC therapy may be able to overcome the effect of this prognostic factor or it may not be a prognostic factor in this setting.

6/3,AB/47 (Item 47 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

11116413 21130759 PMID: 11236028
The role of **HER-2** expression in predicting response to therapy in breast cancer.
Mass R
Oncology Center, Genentech BioOncology, Inc, So San Francisco, CA 94080-4990, USA.
Seminars in oncology (United States) Dec 2000, 27 (6 Suppl 11) p46-52; discussion 92-100, ISSN 0093-7754 Journal Code: 0420432
Document type: Journal Article; Review; Review, Tutorial
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
HER-2 expression may have predictive value regarding response to therapeutic interventions in breast cancer. A number of reports describe the interaction of **HER-2** overexpression and tamoxifen, but data are inconclusive. Chemotherapy trials have supported an interaction between **HER-2** overexpression and chemotherapy sensitivity (cyclophosphamide/methotrexate/5-fluorouracil **resistance** and doxorubicin sensitivity) which is compelling. More recently, **HER-2** has been the target for Food and **Drug** Administration-approved antibody therapy, trastuzumab (Herceptin; Genentech, Inc, South San

Francisco, CA). The Clinical Trials Assay, a scoring system for tumor material, has been used successfully in the trastuzumab clinical development program. As many of the early studies evaluating the role of **HER-2** were retrospective, controlled prospective studies are needed to best determine the value of trastuzumab in the adjuvant clinical setting.

6/3,AB/48 (Item 48 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

11116411 21130757 PMID: 11236026
Ongoing and planned trials of hormonal therapy and trastuzumab.
Nicholson B P
Vanderbilt Ingram Cancer Center, Nashville, TN 37232, USA.
Seminars in oncology (United States) Dec 2000, 27 (6 Suppl 11) p33-7; discussion 92-100, ISSN 0093-7754 Journal Code: 0420432
Document type: Journal Article; Review; Review, Tutorial
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed

Studies with human breast cancer cell lines have shown a causal association between overexpression of the **HER-2/neu** proto-oncogene receptor and the acquisition of **resistance** to tamoxifen. Some clinical studies also indicate that patients with tumors showing high **HER-2** levels or high levels of the circulating ectodomain of **HER-2** may have a lower response to tamoxifen compared with tumors with low **HER-2** levels or low circulating ectodomain. Treatment with anti-**HER-2** antibodies seems to restore tamoxifen activity in some experimental systems. However, whether anti-**HER-2** therapies will increase tamoxifen action and/or reverse this putative oncogene-mediated **resistance** in patients with estrogen receptor-positive, hormone-dependent tumors, is unclear. We are conducting a phase II trial of a humanized anti-**HER-2** monoclonal antibody, trastuzumab (Herceptin; Genentech, Inc, South San Francisco, CA) in combination with tamoxifen in patients with estrogen receptor-positive metastatic breast cancer. Other prospective randomized clinical trials are needed to directly evaluate the contribution of **HER-2** signaling to antiestrogen **resistance** in vivo.

6/3,AB/49 (Item 49 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

11094659 21094738 PMID: 11167089
Closing remarks and treatment guidelines.
Piccart M
Institut Jules Bordet, Unite de Chimiotherapie, 1 Rue Heger Bordet, B-1000 Brussels, Belgium. piccart@ulb.ac.be
European journal of cancer (Oxford, England : 1990) (England) Jan 2001, 37 Suppl 1 pS30-3, ISSN 0959-8049 Journal Code: 9005373
Document type: Journal Article; Review; Review, Tutorial
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed

The human epidermal growth factor receptor HER2 or C-erbB-2/**neu** is a tyrosine kinase membrane receptor, which when activated, induces a phosphorylation cascade in cytoplasmic kinases leading to increased protein transcription and cellular growth. HER2 plays an important role in the biology of breast cancer, an observation that has led to the selection of HER2 as a potential target for breast cancer treatment. Trastuzumab (Herceptin) is the first anti-HER2 monoclonal antibody that has shown a survival benefit in metastatic breast cancer patients with HER2-positive tumours (Norton et al., Proc ASCO 2000 18, 127a (abstract 483)). Tumour

HER2 status should no longer be ignored because of its direct implications for the optimal management of breast cancer patients. A high priority for future research is to refine and standardise HER2 testing in order to minimise false-negative results. Furthermore, this procedure would overcome current issues relating to test reproducibility between pathology laboratories and definitions of HER2 positivity. In the meantime, a HER2-positive status on testing using any approved technique has implications for clinical practice (Fig. 1). The treatment algorithm given in Fig. 1 considers the lack of level 1, evidence-based studies that demonstrate convincingly the value of HER2 as a predictive marker for **resistance** or sensitivity to classic forms of breast cancer therapy (Piccart et al., Eur J Cancer 2000, 36, 1755-1761). In addition, the algorithm incorporates the available data from 1999-2000, which were generated from prospective trials exploring the value of trastuzumab both as a single agent and in combination with chemotherapy.

6/3,AB/50 (Item 50 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

11033258 21027950 PMID: 11156254

Response and determinants of sensitivity to paclitaxel in human non-small cell lung cancer tumors heterotransplanted in nude mice.

Perez-Soler R; Kemp B; Wu Q P; Mao L; Gomez J; Zeleniuch-Jacquotte A; Yee H; Lee J S; Jagirdar J; Ling Y H

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Clinical cancer research : an official journal of the American Association for Cancer Research (United States) Dec 2000, 6 (12) p4932-8, ISSN 1078-0432 Journal Code: 9502500

Contract/Grant No.: CA 50270; CA; NCI; CA16087; CA; NCI; CA60496; CA; NCI

Document type: Journal Article

Languages: ENGLISH

Main Citation Owner: NLM

Record type: Completed

The lack of tumor models that can reliably predict for response to anticancer agents remains a major deficiency in the field of experimental cancer therapy. Although heterotransplants of certain human solid tumors can be successfully grown in nude mice, they have never been appropriately explored for prediction of in vivo chemosensitivity to anticancer agents. We determined the tumor response rate and studied the influence of several biological and molecular tumor parameters on the in vivo sensitivity to paclitaxel in a series of heterotransplanted human non-small cell lung cancer (NSCLC) tumors. One hundred consecutive resected NSCLC tumors were heterotransplanted s.c. in nude mice. The in vivo sensitivity to i.v. paclitaxel (60 mg/kg every 3 weeks) was studied in 34 successfully grown heterotransplants. Treatment started when the tumors reached a size of 5 mm in diameter, and strict standard clinical criteria (>50% shrinkage in tumor weight or cross-sectional surface) were used to define tumor response. Baseline multidrug **resistance** protein (MRP), **Her-2/neu**, and epidermal growth factor receptor (EGFR) expression, and pre- and posttherapy bax and bcl-2 expression were determined by Western blot analysis. p53 status was determined by sequencing. The overall take rate was 46% (95% confidence interval, 36-56%) and was significantly higher ($P < 0.05$) for squamous carcinoma tumors (75%) than for adenocarcinoma tumors (30%) and bronchoalveolar tumors (23%). The heterotransplants were morphologically very similar to the original tumors. The response rate to paclitaxel was 21% (95% confidence interval, 9-38%). Baseline tumor parameters associated with response were no **Her-2/neu** expression (none of the responding tumors expressed **Her-2/neu** versus 48% of the nonresponding tumors, $P = 0.05$) and baseline bcl-2 expression (all responding tumors expressed bcl-2 versus only 43% of the nonresponding tumors, $P = 0.02$). There was a trend toward a higher response rate in bax-positive tumors, and MRP- and EGFR-negative tumors,

but it was not statistically significant. The response was independent of baseline p53 status and baseline mitotic index. Responding tumors had a higher bax/bcl-2 ratio 24 h after therapy, but the difference was only marginally significant (2.8 for responding tumors versus 1.1 for nonresponding tumors, P = 0.07). The extent of mitotic arrest at 24 h after therapy was not associated with response. Human NSCLC heterotransplants are morphologically identical to the original tumors and have a response rate to paclitaxel that is equivalent to that reported in Phase II studies in patients with advanced NSCLC treated with single-agent paclitaxel. NSCLC heterotransplants deserve to be explored to evaluate new agents for lung cancer and to predict clinical response on an individual basis in selected groups of patients.

6/3,AB/51 (Item 51 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10950682 20511594 PMID: 11059787
Inhibition of HER2/**neu** (erbB-2) and mitogen-activated protein kinases enhances tamoxifen action against HER2-overexpressing, tamoxifen-**resistant** breast cancer cells.
Kurokawa H; Lenferink A E; Simpson J F; Pisacane P I; Sliwkowski M X; Forbes J T; Arteaga C L
Department of Medicine, Vanderbilt University School of Medicine, Nashville, Tennessee 37232, USA.
Cancer research (UNITED STATES) Oct 15 2000, 60 (20) p5887-94, ISSN 0008-5472 Journal Code: 2984705R
Contract/Grant No.: CA68485; CA; NCI; R01 CA80195; CA; NCI
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
HER2/**neu** (erbB-2) overexpression has been causally associated with tamoxifen **resistance** in human breast cancer cells. Forced expression of HER2 in MCF-7 breast cancer cells resulted in mitogen-activated protein kinase (MAPK) hyperactivity and tamoxifen **resistance**. Inhibition of HER2 and MAPKs with AG1478 and U0126, respectively, as well as dominant-negative MEK-1/2 constructs restored the inhibitory effect of tamoxifen on estrogen receptor (ER)-mediated transcription and cell proliferation. Both AG1478 and U0126 also restored the tamoxifen-mediated association of ER with nuclear receptor corepressor (N-CoR) in the antiestrogen-**resistant** MCF-7 cells. Treatment with a combination of tamoxifen and a HER2 kinase inhibitor reduced tumor MAPK activity and markedly prevented growth of HER2-overexpressing MCF-7 xenografts in athymic mice. Thus, blockade of HER2 and MAPK signaling may enhance tamoxifen action and abrogate antiestrogen **resistance** in human breast cancer.

6/3,AB/52 (Item 52 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10925055 20487640 PMID: 11032587
HER-2/neu and p53 expression versus tamoxifen **resistance** in estrogen receptor-positive, node-positive breast cancer.
Berry D A; Muss H B; Thor A D; Dressler L; Liu E T; Broadwater G; Budman D R; Henderson I C; Barcos M; Hayes D; Norton L
University of Texas M.D. Anderson Cancer Center, Houston, TX 77030, USA. dberry@odin.mdacc.tmc.edu
Journal of clinical oncology : official journal of the American Society of Clinical Oncology (UNITED STATES) Oct 15 2000, 18 (20) p3471-9, ISSN 0732-183X Journal Code: 8309333
Contract/Grant No.: CA31946; CA; NCI

Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
PURPOSE: An association between the overexpression of proto-oncogene **HER-2/neu** and **resistance** to tamoxifen in estrogen receptor (ER)-positive primary and metastatic breast cancer has been suggested. We examine a possible interaction between **HER-2/neu** or p53 expression and tamoxifen effectiveness in patients with ER-positive, node-positive disease treated with cyclophosphamide, doxorubicin, and fluorouracil in a large adjuvant chemotherapy trial (Cancer and Leukemia Group B [CALGB] 8541). Tamoxifen assignment was not randomized-physician discretion was used for premenopausal and postmenopausal women. Trial protocol then specified assignment to postmenopausal women with ER-positive tumors, although not all took tamoxifen. PATIENTS AND METHODS: CALGB 8541 assessed **HER-2/neu** expression in patients with ER-positive disease by immunohistochemistry (IHC) and fluorescent in situ hybridization (FISH) and amplification by differential polymerase chain reaction (PCR). IHC assessed expression of p53. Univariate and multivariate proportional hazards models assessed tamoxifen-**HER-2/neu** status interactions and tamoxifen-p53 status interactions. RESULTS: **HER-2/neu** status was available for 651 patients with ER-positive disease; 650, 608, and 353 patients were assessed by IHC, PCR, and FISH, respectively. Approximately one half received tamoxifen. Reduction in risk of disease recurrence or death resulting from tamoxifen was approximately 37% (32% with overexpression and 39% with normal expression of **HER-2/neu**; n = 155 by IHC). The tamoxifen-**HER-2/neu** status interaction was not significant in multivariate analysis of all three **HER-2/neu** assessment methods. Tamoxifen-p53 interaction did not significantly predict outcome. CONCLUSION: Disease-free and overall survival benefit of tamoxifen in patients with ER-positive, node-positive breast cancer does not depend on **HER-2/neu** or p53 status. Our data suggest that neither **HER-2/neu** nor p53 expression should be used to determine assignment of tamoxifen.

6/3,AB/53 (Item 53 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10924442 20500546 PMID: 11049051
State-of-the-art chemotherapy for advanced breast cancer.
Piccart M J; Awada A
Division of Chemotherapy, Institut Jules Bordet, Brussels, Belgium.
Seminars in oncology (UNITED STATES) Oct 2000, 27 (5 Suppl 9) p3-12,
ISSN 0093-7754 Journal Code: 0420432
Document type: Journal Article; Review; Review, Tutorial
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
Several recent advances have led to accelerated progress in breast cancer therapy. The development of new drugs with novel mechanisms of action, such as the taxanes, or oral bioavailability, such as capecitabine, has expanded the horizons of available chemotherapy. The use of tumor-related proteins or genes as markers of sensitivity or **resistance** to systemic therapy may allow for more predictable outcomes. Finally, the emergence of biological therapies such as the HER2/**neu** monoclonal antibody trastuzumab (Herceptin; Genentech, Inc, So. San Francisco, CA) represents an exciting new direction that opens doors to new concepts in antitumor therapy. This report will review the most exciting possibilities for expanding the field of breast cancer management.

6/3,AB/54 (Item 54 from file: 155)

DIALOG(R)File 155:MEDLINE(R)

10911938 20461199 PMID: 11004679
A novel recombinant fusion toxin targeting **HER-2/NEU** -over-expressing cells and containing human tumor necrosis factor.
Rosenblum M G; Horn S A; Cheung L H
Immunopharmacology and Targeted Therapy Section, Department of Bioimmunotherapy, University of Texas M.D. Anderson Cancer Center, Houston, Texas 77030, USA. mrosenbl@notes.mdacc.tmc.edu
International journal of cancer. Journal international du cancer (UNITED STATES) Oct 15 2000, 88 (2) p267-73, ISSN 0020-7136 Journal Code: 0042124
Contract/Grant No.: CA 16672; CA; NCI
Erratum in Int J Cancer. 2000 Dec 15;88(6) 1009
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
Over-expression of the proto-oncogene HER2/**neu** in breast cancer and certain other tumors appears to be a central mechanism that may be partly responsible for cellular progression of the neoplastic phenotype. Transfection of mammalian cells and over-expression of HER2/**neu** appears to result in reduced sensitivity to the cytotoxic effects of tumor necrosis factor (TNF) and reduced sensitivity to immune effector killing. The single-chain recombinant antibody sFv23 recognizes the cell-surface domain of HER2/**neu**. The cDNA for this antibody was fused to the cDNA encoding human TNF, and this sFv23/TNF fusion construct was cloned into a plasmid for expression in Escherichia coli. The fusion protein was expressed and purified by ion-exchange chromatography. SDS-PAGE demonstrated a single band at the expected m.w. (43 kDa). Western analysis confirmed the presence of both the antibody component and the TNF component in the final fusion product. The fusion construct was tested for TNF activity against L-929 cells and found to have biological activity similar to that of authentic TNF (SA 420 nM). The scFv23/TNF construct bound to SKBR-3 (HER2-positive) but not to A-375 human melanoma (HER2-negative) cells. Cytotoxicity studies against log-phase human breast carcinoma cells (SKBR-3-HP) over-expressing HER2/**neu** demonstrate that the sFv23/TNF fusion construct was 1, 000-fold more active than free TNF. Tumor cells expressing higher levels of HER2/**neu** (SKBR-3-LP) were relatively **resistant** to both the fusion construct and native TNF. These studies suggest that fusion constructs targeting the HER2/**neu** surface domain and containing TNF are more effective cytotoxic agents in vitro than native TNF and may be effective against tumor cells expressing intermediate, but not high, levels of HER2/**neu**. Copyright 2000 Wiley-Liss, Inc.

6/3,AB/55 (Item 55 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10867125 20441566 PMID: 10987282
Suppression of ethylnitrosourea-induced schwannoma development involves elimination of **neu**/erbB-2 mutant premalignant cells in the **resistant** BDIV rat strain.
Kindler-Rohrborn A; Kind A B; Koelsch B U; Fischer C; Rajewsky M F
Institute of Cell Biology (Cancer Research), University of Essen Medical School and West German Cancer Center Essen.
Cancer research (UNITED STATES) Sep 1 2000, 60 (17) p4756-60, ISSN 0008-5472 Journal Code: 2984705R
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
Contrary to the response of rats of the highly sensitive inbred strain BDIX, BDIV rats are **resistant** to the induction of malignant

schwannomas by exposure to the alkylating N-nitroso carcinogen N-ethyl-N-nitrosourea (EtNU). In BDIX rats, a point mutation at nucleotide 2012 in the transmembrane region of the **neu**/erbB-2 gene has proved to be a very early marker of initiated Schwann precursor cells with an elevated risk of malignant transformation, and is diagnostic of the resulting schwannomas. To gain insight into the cellular and molecular mechanisms responsible for the **resistance** of the BDIV strain, comparative quantitative **neu** mutation analyses combined with histomorphological studies were performed on the trigeminal nerves of EtNU-treated BDIV and BDIX rats as well as on their (BDIX x BDIV) F1 progeny. It was found that **neu**-mutant Schwann cells are initially present at comparable frequency in the trigeminal nerves of both **resistant** and sensitive animals. Contrasting with the progressive multiplication of mutant Schwann cells in BDIX trigeminal nerves, however, the numbers of mutant cells began to decrease during the intermediary phase of the carcinogenic process in BDIV animals, and premalignant **neu** -mutant cells were no longer detectable by the time BDIX rats developed full-blown trigeminal schwannomas. The **resistance** of BDIV rats thus involves the elimination of initiated **neu**-mutant Schwann cells during the postinitiation period of EtNU-induced schwannomagenesis via mechanisms that remain to be clarified.

6/3,AB/56 (Item 56 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10780703 20340777 PMID: 10882863

'Accidental' anti-angiogenic drugs. anti-oncogene directed signal transduction inhibitors and conventional chemotherapeutic agents as examples.

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European journal of cancer (Oxford, England : 1990) (ENGLAND) Jun 2000, 36 (10) p1248-57, ISSN 0959-8049 Journal Code: 9005373
Contract/Grant No.: CA41233; CA; NCI
Document type: Journal Article; Review; Review, Tutorial
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed

A number of drugs currently being tested in clinical trials as possible angiogenesis inhibitors were not originally developed with the intention of suppressing tumour angiogenesis. Thalidomide and interferon alpha are obvious examples of such drugs. This list of 'accidental' angiogenesis inhibitors may include established agents such as conventional cytotoxic chemotherapeutic drugs as well as the new generation of anticancer drugs known as anti-oncoprotein signal transduction inhibitors. With respect to the former, the potential of such drugs to inhibit angiogenesis could be the result of their ability to cause collateral damaging effects on cycling endothelial cells found in newly formed blood vessels, or inhibiting other vital endothelial cell functions necessary for angiogenesis. The antitumour vascular side-effects of chemotherapy may be optimised by administering such drugs continuously on a more frequent (e.g. weekly or even daily) basis at levels well below the maximum tolerated dose (MTD), especially when this is done in combination with newly developed anti-angiogenic drugs such as vascular endothelial cell growth factor (VEGF) receptor blocking antibodies. This strategy may minimise or delay the problems of host toxicity and acquired **drug resistance** . The possibility of anti-angiogenic effects mediated by signal transduction inhibitors such as ras farnesyltransferase inhibitors (ras FTI's), or drugs which block receptor tyrosine kinases (e.g. ErbB2/**neu**) such as Herceptin, may be the consequence of such oncogenes inducing or upregulating various pro-angiogenic molecules such as VEGF (vascular endothelial cell growth

factor) in tumour cells. Hence, treatment of tumour cells with such drugs can lead to downregulation of tumour cell-associated VEGF expression and this can contribute to an anti-angiogenic effect of the **drug** in vivo. In addition, some of these drugs may also affect certain 'activated' endothelial cell functions directly so as to block angiogenesis. An awareness of the potential of such conventional or experimental anticancer drugs to affect tumour growth through blockade or suppression of angiogenesis has implications for how anticancer drugs may be used clinically, either alone, or in combination with other drugs to optimally treat cancer.

6/3,AB/57 (Item 57 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10764692 20288952 PMID: 10830140
Current approaches and future strategies for pancreatic carcinoma.
Wolff R A; Chiao P; Lenzi R; Pisters P W; Lee J E; Janjan N A; Crane C H; Evans D B; Abbruzzese J L
University of Texas M.D. Anderson Cancer Center, Houston 77030-4095, USA.
Investigational new drugs (UNITED STATES) Feb 2000, 18 (1) p43-56, ISSN 0167-6997 Journal Code: 8309330
Document type: Journal Article; Review; Review, Tutorial
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
Pancreatic cancer is a lethal disease characterized by local invasion and early dissemination. It is **resistant** to conventional surgical, radiotherapeutic, and chemotherapeutic modalities. These interventions have had minimal impact on overall survival with very few patients enjoying long term survival. Over the past few years, 2'difluoro-2'deoxycytidine (gemcitabine) has demonstrated modest activity in this disease and investigations are proceeding to expand its role in combination with radiotherapy and other chemotherapeutic agents. In addition, the identification of the molecular defects underlying this disease has suggested molecular targets for the design of rational systemic therapy. These targets include matrix metalloproteinases, K-ras, HER2/**neu**, p53, and the epidermal growth factor receptor. Current and future clinical trials designed to improve the survival of patients with pancreatic cancer will be discussed.

6/3,AB/58 (Item 58 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10726472 20267219 PMID: 10809222
Biologic and clinical significance of **HER-2/neu** (cerbB-2) in breast cancer.
Sahin A A
Department of Pathology, The University of Texas M.D. Anderson Cancer Center, Houston 77030, USA.
Advances in anatomic pathology (UNITED STATES) May 2000, 7 (3) p158-66, ISSN 1072-4109 Journal Code: 9435676
Document type: Journal Article; Review; Review, Tutorial
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
HER-2/neu (also known as c-erbB-2) oncogene is a member of the epidermal growth factor receptor family and its amplification is one of the most common genetic alterations associated with human breast cancer. Preclinical studies have suggested that **HER-2/neu** overexpression enhances metastatic potential of breast cancer cells. Although some discrepancies exist in clinical studies, in general, **HER-2/neu** amplification is found to be associated with

more aggressive clinicopathologic features. **HER-2/neu** amplification is also associated with **drug resistance** or sensitivity to specific chemotherapy and hormonal therapy regimens. Advances in breast cancer therapies in recent years have moved towards the development of tumor-specific targeted therapies. Monoclonal antibodies directed against **HER-2/neu** have been developed and used in clinical practice. These developments necessitate a reliable assay for assessment of **HER-2/neu** . This article is a review of biologic and clinical significance of **HER-2/neu** and summarizes **HER-2/neu** detection methods.

6/3,AB/59 (Item 59 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10701030 20245673 PMID: 10781891
Reversal of **HER-2** over-expression renders human ovarian cancer cells highly **resistant** to taxol.
Aigner A; Hsieh S S; Malerczyk C; Czubayko F
Department of Pharmacology and Toxicology, Philipps University, Forschungseinrichtungen, Karl-von-Frisch-Str. 1, 35033 Medizinische, Marburg, Germany.
Toxicology (IRELAND) Apr 3 2000, 144 (1-3) p221-8, ISSN 0300-483X Journal Code: 0361055
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
Currently, the treatment options for advanced ovarian cancer are limited. Thus, the majority of the patients are treated with drugs with considerable side effects but in many cases without clinical benefit. The relationship between activation of an oncogene like the **HER-2** receptor and **drug** sensitivity, is of considerable interest as this molecular marker may allow to better predict response to chemotherapy. The aim of this study was to evaluate whether over-expression of the **HER-2** receptor would modulate **drug** responsiveness to doxorubicin, cisplatin and taxol in ovarian cancer cells. An anti-**HER-2** -targeted ribozyme approach was used to abrogate **HER-2** expression in human SK-OV-3 ovarian cancer cells. SK-OV-3 cells expressing very low residual levels of **HER-2** protein, were then assessed for their sensitivity to doxorubicin, cisplatin and taxol and compared to control cells. **HER-2** expression had no effect on the cytotoxicity of doxorubicin (IC50=10 nM) or cisplatin (IC50=5 microM) in proliferation assays. In contrast, the sensitivity to taxol was increased approximately 70-fold in SK-OV-3 ovarian cancer cells expressing high levels of **HER-2** (IC50=10(-5) nM) compared to **HER-2** depleted cells (IC50=7x10(-4) nM). If these findings can be confirmed in patients, it could be possible that **HER-2** expression may serve as a marker for response to taxol treatment in ovarian cancer patients.

6/3,AB/60 (Item 60 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10696958 20229352 PMID: 10768865
Blocking **HER-2**/HER-3 function with a dominant negative form of HER-3 in cells stimulated by heregulin and in breast cancer cells with **HER-2** gene amplification.
Ram T G; Schelling M E; Hosick H L
School of Biological Science, Washington State University, Pullman 99164-4236, USA. tram@mail.wsu.edu
Cell growth & differentiation : the molecular biology journal of the American Association for Cancer Research (UNITED STATES) Mar 2000, 11 (3) p173-83, ISSN 1044-9523 Journal Code: 9100024

Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
Amplification and overexpression of the **HER-2** (**neu**/erbB-2) gene in human breast cancer are clearly important events that lead to the transformation of mammary epithelial cells in approximately one-third of breast cancer patients. Heterodimer interactions between **HER-2** and HER-3 (erbB-3) are activated by **neu** differentiation factor/heregulin (HRG), and **HER-2** /HER-3 heterodimers are constitutively activated in breast cancer cells with **HER-2** gene amplification. This indicates that inhibition of **HER-2**/HER-3 heterodimer function may be an especially effective and unique strategy for blocking the **HER-2** -mediated transformation of breast cancer cells. Therefore, we constructed a bicistronic retroviral expression vector (pCMV-dn3) containing a dominant negative form of HER-3 in which most of the cytoplasmic domain was removed for introduction into cells. By using a bicistronic retroviral vector in which the antibiotic **resistance** gene and the gene of interest are driven by a single promoter, we attained 100% coordinate coexpression of antibiotic **resistance** with the gene of interest in target cell populations. Breast carcinoma cells with **HER-2** gene amplification (21 MT-1 cells) and normal mammary epithelial cells without **HER-2** gene amplification from the same patient (H16N-2 cells) were infected with pCMV-dn3 and assessed for **HER-2**/ HER-3 receptor tyrosine phosphorylation, p85PI 3-kinase and SHC protein activation, growth factor-dependent and -independent proliferation, and transformed growth in culture. Dominant negative HER-3 inhibited the HRG-induced activation of **HER-2**/HER-3 and signaling in H16N-2 and 21 MT-1 cells as well as the constitutive activation of **HER-2** /HER-3 and signaling in 21 MT-1 cells. Responses to exogenous HRG were strongly inhibited by dominant negative HER-3. In contrast, the proliferation of cells stimulated by epidermal growth factor was not apparently affected by dominant negative HER-3. The growth factor-independent proliferation and transformed growth of 21 MT-1 cells were also strongly inhibited by dominant negative HER-3 in anchorage-dependent and independent growth assays in culture. Furthermore, the HRG-induced or growth factor-independent proliferation of 21 MT-1 cells was inhibited by dominant negative HER-3, whereas the epidermal growth factor-induced proliferation of these cells was not: this indicates that dominant negative HER-3 preferentially inhibits proliferation induced by **HER-2**/HER-3.

6/3,AB/61 (Item 61 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10681111 20222346 PMID: 10761709
Interrelationships between cellular nucleotide excision repair, cisplatin cytotoxicity, **HER-2/neu** gene expression, and epidermal growth factor receptor level in non-small cell lung cancer cells.
Tsai C M; Chang K T; Li L; Perng R P; Yang L Y
Chest Department, Veterans General Hospital-Taipei, Shih-pai, Taiwan. cmtsai@vghtpe.gov.tw
Japanese journal of cancer research : Gann (JAPAN) Feb 2000, 91 (2) p213-22, ISSN 0910-5050 Journal Code: 8509412
Contract/Grant No.: CA-68137; CA; NCI
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
Nucleotide excision repair (NER) is a major repair mechanism for DNA lesions induced by cisplatin. Overexpressions of epidermal growth factor receptor (EGFR) and **HER-2/neu** have been reported to

affect the sensitivity of certain human cancer cells to cisplatin, presumably by modification of DNA repair activity through interference with NER. Using an in vitro repair assay, we investigated NER activity of cisplatin-induced DNA lesions in a panel of 16 non-small cell lung cancer (NSCLC) cell lines. The interrelationships between NER activity, cisplatin sensitivity, **HER-2/neu** expression and EGFR level, were also analyzed. The results showed that high NER activity was closely correlated with cisplatin **resistance** and high levels of **HER-2/neu** expression ($P<0.05$). Analysis of the relationships between EGFR level and each of the other three parameters revealed no statistically significant correlations (all P values were >0.05 by Spearman rank correlation), but a trend of association (all the values of proportion of accordance were > or =62.5% by using a 2x2 contingency table). These results suggest that NER activity may play an important role in the cisplatin **resistance** of NSCLC cells and there may be an association between enhanced NER activity and high levels of p185neu and probably EGFR in NSCLC cells. The finding that high levels of EGFR showed very little influence on the relationship between p185neu and cisplatin **resistance** suggests that EGFR may be a less crucial factor in modulating the chemoresistance of NSCLC cells when compared with **HER-2/neu**.

6/3,AB/62 (Item 62 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10638653 20179909 PMID: 10713122
HER-2/neu blocks tumor necrosis factor-induced apoptosis via the Akt/NF-kappaB pathway.
Zhou B P; Hu M C; Miller S A; Yu Z; Xia W; Lin S Y; Hung M C
Department of Molecular and Cellular Oncology, Breast Cancer Basic Research Program, The University of Texas M. D. Anderson Cancer Center, Houston, Texas 77030, USA.
Journal of biological chemistry (UNITED STATES) Mar 17 2000, 275 (11) p8027-31, ISSN 0021-9258 Journal Code: 2985121R
Contract/Grant No.: CA 16672; CA; NCI; R01-CA58880; CA; NCI; R01-CA77858; CA; NCI
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
Overexpression of **HER-2/neu** correlates with poor survival of breast and ovarian cancer patients and induces **resistance** to tumor necrosis factor (TNF), which causes cancer cells to escape from host immune defenses. The mechanism of **HER-2/neu**-induced TNF **resistance** is unknown. Here we report that **HER-2/neu** activates Akt and NF-kappaB without extracellular stimulation. Blocking of the Akt pathway by a dominant-negative Akt sensitizes the **HER-2/neu** -overexpressing cells to TNF-induced apoptosis and inhibits IkappaB kinases, IkappaB phosphorylation, and NF-kappaB activation. Our results suggested that **HER-2/neu** constitutively activates the Akt/NF-kappaB anti-apoptotic cascade to confer **resistance** to TNF on cancer cells and reduce host defenses against neoplasia.

6/3,AB/63 (Item 63 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10628519 20162643 PMID: 10697535
Expression of activated c-erbB-2 oncogene induces sensitivity to cisplatin in human gallbladder adenocarcinoma cells.
Boudny V; Murakami Y; Nakano S; Niho Y
First Department of Internal Medicine, Faculty of Medicine, Kyushu

University, Fukuoka, Japan.
Anticancer research (GREECE) Nov-Dec 1999, 19 (6B) p5203-6, ISSN 0250-7005 Journal Code: 8102988
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
Overexpression of the c-erbB-2/**HER-2/neu** protooncogene which encodes for the tyrosine kinase receptor p185neu, has been observed frequently in cisplatin **resistant** human tumors, such as colorectal, breast, and non-small-cell lung cancers, and is known to induce **resistance** to cisplatin (CDDP) in vitro. To confirm a direct relationship between erbB-2 expression and CDDP **resistance** , we examined the role of erbB-2 in the cellular sensitivity to cisplatin using erbB-2 transfected HAG-1 human gallbladder adenocarcinoma cell lines. Three out of four cell lines, which stably expressed ErbB-2 protein (p185neu), did not show CDDP **resistance** but acquired sensitivity to cisplatin, compared to non-transfected cells. This chemosensitivity appears to be inversely correlated with the abundance of p185neu. Although the mechanism still remains unclear, these results suggest that sensitivity to CDDP in erbB-2 expressed cells may vary, depending on the cell type.

6/3,AB/64 (Item 64 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10608482 20142049 PMID: 10678581
Molecular predictive factors for local recurrence and distant metastasis of breast cancer after lumpectomy with postoperative radiation therapy.
Amornmarn R; Bui M M; Prempree T B; Masood S
Department of Pathology, University of Florida Health Science Center, Jacksonville 32209, USA.
Annals of clinical and laboratory science (UNITED STATES) Jan 2000, 30 (1) p33-40, ISSN 0091-7370 Journal Code: 0410247
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
To determine the risk factors associated with the recurrence and metastasis of breast cancer after lumpectomy with postoperative radiation therapy, 112 cases were studied who had been treated during a period of 11 years at the University of Florida Health Science Center/Jacksonville. The patients were evaluated for their age, race, and clinical stage, as well as the tumor grade, stage, histological type, and node involvement. Among these cases, four (4%) recurred locally within a year of treatment; 10 (9%) cases presented with distant metastasis within three years. No obvious clinical risk factors were identified for local recurrence; however, positive-node status seemed to be associated with distant metastasis. The primary tumors of these cases were then studied using immunohistochemical staining to evaluate the potential prognostic value of tumor markers such as estrogen receptor (ER), progesterone receptor (PR), tumor suppressor gene p53, **HER-2/neu** oncogene, and multi-**drug resistance** gene (MDR). The expression of p53 was associated with all local recurrence cases as well as 50% of those who had metastasis. The expression of MDR was observed in 80% of the distant metastatic cases. This preliminary result may warrant further studies on larger number of cases to assess the predictive value of p53 and MDR in the outcome of breast cancers in patients treated with postoperative radiation therapy.

6/3,AB/65 (Item 65 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10595326 20140976 PMID: 10676567

New approaches in cancer treatment.
Sikic B I
Stanford University School of Medicine, California, USA. brandy@stanford.edu
Annals of oncology : official journal of the European Society for Medical Oncology / ESMO (NETHERLANDS) 1999, 10 Suppl 6 p149-53, ISSN 0923-7534 Journal Code: 9007735
Contract/Grant No.: MO1 RR 00070; RR; NCRR; RO1 CA 52168; CA; NCI
Document type: Journal Article; Review; Review, Tutorial
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed

Major advances in cellular biology, genetics, pharmacology and immunology in the past decade are beginning to be translated into progress in cancer treatment. This progress is manifested by new cytotoxic drugs which have recently entered clinical practice (taxanes, topoisomerase I inhibitors, gemcitabine, vinorelbine, new purines), as well as the efficacy of monoclonal antibody therapies against the CD-20 antigen of B-cell lymphomas and the Her2/**neu** oncogene in breast cancer. Several new drugs in development are targeted at reversal or prevention of the multidrug **resistance** mechanism caused by expression of the MDR1 gene (P-glycoprotein). Tumour angiogenesis as a target is being studied in several early clinical trials. As with many other biological therapies, the evaluation of these compounds and their integration with standard therapies presents a major challenge to clinical investigators. The emerging field of genomics and gene expression micro-arrays will provide enormous information about the biology of cancers. This technology offers great opportunities for the discovery of new therapeutic targets, which should provide a basis for the design and evaluation of many new agents in the coming decade.

6/3,AB/66 (Item 66 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10595324 20140974 PMID: 10676565
New developments in chemotherapy of advanced breast cancer.
Lebwohl D E; Canetta R
Bristol-Myers Squibb Pharmaceutical Research Institute, Wallingford, CT, USA.
Annals of oncology : official journal of the European Society for Medical Oncology / ESMO (NETHERLANDS) 1999, 10 Suppl 6 p139-46, ISSN 0923-7534 Journal Code: 9007735
Document type: Journal Article; Review; Review, Tutorial
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed

Anthracyclines and taxanes are the two most active classes of chemotherapy for the treatment of advanced breast cancer. Recent studies have investigated combination therapy including doxorubicin (Dox) and paclitaxel. The efficacy of this combination has been established in a phase III study conducted by ECOG, comparing Dox/paclitaxel versus Dox versus paclitaxel. The combination is superior to Dox or paclitaxel with respect to response rate and time to disease progression, indicating that the combination provides a new standard for the first line treatment of metastatic breast cancer [1]. Phase II studies using higher doses of Dox and using shorter infusions of paclitaxel have suggested the combination can be further optimized; Gianni reported a 94% objective response rate using Dox 60 mg/m2 followed by paclitaxel 175 mg/m2 given over three hours [2]. The more active regimens are associated with enhanced cardiotoxicity; this toxicity can be avoided, however, by limiting the exposure to doxorubicin. The newer regimens have now been moved into phase III studies. Future progress for this disease will depend on the introduction of new agents. Two novel drugs are currently being investigated in randomised phase III trials as potentiators of Dox and/or paclitaxel. One is a

monoclonal antibody from Genentech (Herceptin, trastuzumab) directed at the **HER-2/neu** oncogene, which is overexpressed in > 25% of breast cancers [3]. Recent results indicate that Herceptin in combination with paclitaxel (or with a Dox plus cyclophosphamide regimen) induces a higher response rate (RR) and prolongs the time to disease progression when compared to chemotherapy alone. The second agent N,N-diethyl-2[4-(phenylmethyl)-phenoxy] ethanamine.HCl (DPPE, BMS-217380-01), when combined with Dox, was associated with a higher RR than previously observed with Dox alone [4]. A randomized trial of Dox versus Dox plus DPPE is ongoing. The possible mechanisms underlying chemo-potentiation by these agents are discussed. As new anthracycline/taxane combinations establish themselves in earlier stages of the disease, the need for effective, non-cross **resistant** salvage regimens will emerge.

6/3,AB/67 (Item 67 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10581544 20120249 PMID: 10656456
E1A-mediated paclitaxel sensitization in **HER-2/neu** -overexpressing ovarian cancer SKOV3.ip1 through apoptosis involving the caspase-3 pathway.

Ueno N T; Bartholomeusz C; Herrmann J L; Estrov Z; Shao R; Andreeff M; Price J; Paul R W; Anklesaria P; Yu D; Hung M C

Department of Blood and Marrow Transplantation, The University of Texas M.D. Anderson Cancer Center, Houston 77030, USA.

Clinical cancer research : an official journal of the American Association for Cancer Research (UNITED STATES) Jan 2000, 6 (1) p250-9, ISSN 1078-0432 Journal Code: 9502500

Contract/Grant No.: CA58880; CA; NCI; CA76450-1; CA; NCI; CA77858; CA; NCI

Document type: Journal Article

Languages: ENGLISH

Main Citation Owner: NLM

Record type: Completed

HER-2/neu-overexpressing breast cancer cells are more **resistant** to the chemotherapeutic agent paclitaxel (Taxol) than low-**HER-2/neu** -expressing breast cancer cells, and the adenoviral type 5 EIA can down-regulate **HER-2/neu** overexpression. Therefore, in this study, we asked (a) whether EIA might sensitize response to paclitaxel in human **HER-2/neu** -overexpressing ovarian cancer cells, and, if so, what is the mechanism responsible; and (b) whether this enhanced chemosensitivity would translate into a therapeutic effect in an ovarian cancer xenograft model. Consequently, we demonstrated that: (a) adenovirus type 5 E1A could enhance the sensitivity of paclitaxel in paclitaxel-**resistant HER-2/neu** -overexpressing human ovarian cancer cells in vitro by inducing apoptosis, (b) this induction was heavily dependent on activation of the caspase-3 pathway, and (c) nude mice bearing i.p. **HER-2/neu** -overexpressing human ovarian cancer cells and treated with both paclitaxel and E1A gene therapy survived significantly longer than did mice treated only with paclitaxel or E1A gene therapy. Thus, we concluded that the E1A gene enhanced both the in vitro and in vivo sensitivity of paclitaxel in paclitaxel-**resistant HER-2/ neu** -overexpressing ovarian cancer SKOV3.ipl cells. Because a Phase I clinical trial using E1A gene targeted to **HER-2/neu** down-regulation has recently been completed, the current study also provided a scientific basis to further develop a novel therapy that combines paclitaxel and E1A gene therapy and its testing in a Phase II trial.

6/3,AB/68 (Item 68 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10567826 20097983 PMID: 10634517
Acquired antiestrogen **resistance** in MCF-7 human breast cancer sublines is not accomplished by altered expression of receptors in the ErbB-family.
Larsen S S; Egeblad M; Jaattela M; Lykkesfeldt A E
Department of Tumor Endocrinology, Institute of Cancer Biology, Danish Cancer Society, Copenhagen. ssl@cancer.dk
Breast cancer research and treatment (NETHERLANDS) Nov 1999, 58 (1) p41-56, ISSN 0167-6806 Journal Code: 8111104
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
Development of acquired **resistance** against antiestrogen treatment is a serious problem in human breast cancer, and knowledge of alterations resulting in **resistance** is important for selection of further treatment. To mimic the clinical situation we have established a series of MCF-7 human breast cancer cell lines by long term treatment with the antiestrogens tamoxifen, ICI 164,384, and ICI 182,780. Common for these cell lines is a decreased expression of the estrogen receptor alpha (ER alpha). In human breast cancer, lack of response to endocrine therapy is often associated with decreased expression of the estrogen receptor and increased expression of epidermal growth factor receptor (EGFR) and/or **HER-2/neu** (ErbB-2). Our antiestrogen **resistant** cell lines did not express altered levels of EGFR, **HER-2/neu**, ErbB-3, or ErbB-4. Estrogen and antiestrogen regulation of **HER-2/neu** expression was essentially similar in parent and **resistant** MCF-7 cells. Treatment with antibodies to **HER-2/neu** (Herceptin) did not affect growth of MCF-7 cells or **resistant** cells, indicating that in this in vitro model system, acquired antiestrogen **resistance** does not emerge from activation of the **HER-2/neu** signaling pathway. In MCF-7 cells transfected with **HER-2/neu** and/or ErbB-3, overexpression alone did not result in **resistance** . However, addition of heregulinl-betal abolished the inhibitory activity of ICI 182,780 on both vector and **HER-2/neu** /ErbB-3 transfected MCF-7 cells, demonstrating that activation of the **HER-2/neu** receptor signaling pathway can override the growth inhibitory effect of ICI 182,780.

6/3,AB/69 (Item 69 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10567601 20097049 PMID: 10631474
Cisplatin-refractory, HER2/**neu** -expressing germ-cell cancer: induction of remission by the monoclonal antibody Trastuzumab.
Kollmannsberger C; Pressler H; Mayer F; Kanz L; Bokemeyer C
Annals of oncology : official journal of the European Society for Medical Oncology / ESMO (NETHERLANDS) Nov 1999, 10 (11) p1393-4, ISSN 0923-7534 Journal Code: 9007735
Document type: Letter
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed

6/3,AB/70 (Item 70 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10473282 20012811 PMID: 10544071
Chemo-signal therapy, an emerging new approach to modify **drug resistance** in breast cancer.
Pusztai L; Esteva F J; Cristofanilli M; Hung M C; Hortobagyi G N

Department of Breast Medical Oncology, The University of Texas MD Anderson Cancer Center, 1515 Holcombe Blvd, Houston, TX 77030, USA.
Cancer treatment reviews (ENGLAND) Oct 1999, 25 (5) p271-7, ISSN 0305-7372 Journal Code: 7502030
Document type: Journal Article; Review; Review, Tutorial
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
Recent advances in understanding how response or **resistance** to cytotoxic drugs develops at the cellular level resulted in the development of novel, non-cytotoxic agents that modulate response the chemotherapy. 'Chemo-signal therapy', the combination of chemotherapy with cellular response modifiers, is a very promising new treatment modality that has entered the arena of clinical trials. Clinical experience with the anti-**HER-2** antibody, trastuzumab, in breast cancer has demonstrated that manipulation of growth factor signalling can enhance sensitivity to cytotoxic drugs in a clinically meaningful way. Several other agents that were designed to modulate response to chemotherapy are currently in early phases of clinical **drug** development. It is likely that some of these new molecules will have a major impact on how chemotherapy will be given in the next decade. This paper will review current clinical research with a select group of chemotherapy response modifiers. We will focus on agents that modulate signal transduction, oncogene expression and apoptosis with an emphasis on breast cancer. Copyright 1999 Harcourt Publishers Ltd.

6/3,AB/71 (Item 71 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10470753 20007445 PMID: 10541432
Sustained mitogen-activated protein kinase activation is induced by transforming erbB receptor complexes.
Wu C J; Qian X; O'Rourke D M
Department of Pathology and Laboratory Medicine, University of Pennsylvania School of Medicine, Philadelphia 19104, USA.
DNA and cell biology (UNITED STATES) Oct 1999, 18 (10) p731-41, ISSN 1044-5498 Journal Code: 9004522
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
We used a genetic approach to characterize features of mitogen-activated protein kinase (MAPK) activation occurring as a consequence of expression of distinct erbB receptor combinations in transformed human cells. Kinase-deficient erbB proteins reduced epidermal growth factor (EGF)-induced tyrosine phosphorylation of endogenous Shc proteins and also reduced immediate and sustained EGF-induced ERK MAPK activities in human glioblastoma cells, although basal ERK MAPK activities were unaffected. Basal and EGF-induced JNK and p38 MAPK kinase activities were equivalent in parental cancer cells and EGFR-inhibited subclones. When ectopically overexpressed in murine fibroblasts and human glioblastoma cells, a constitutively activated human EGF receptor oncoprotein (deltaEGFR) induced EGF-independent elevation of basal ERK MAPK activity. Basal JNK MAPK kinase activity was also specifically induced by deltaEGFR, which correlated with increased phosphorylation of a 54-kDa JNK2 protein observed in deltaEGFR-containing cells. The JNK activities in response to DNA damage were comparably increased in cells containing wildtype EGFR or deltaEGFR. Consistent with the notion that transforming erbB complexes induce sustained and unregulated MAPK activities, coexpression of p185(**neu**) and EGFR proteins to levels sufficient to transform murine fibroblasts also resulted in prolonged EGF-induced ERK in vitro kinase activation. Transforming erbB complexes, including EGFR homodimers, deltaEGFR homodimers, and p185(**neu**)/EGFR heterodimers, appear to induce sustained, unattenuated activation of MAPK activities that may contribute

to increased transformation and **resistance** to apoptosis in primary human glioblastoma cells.

6/3,AB/72 (Item 72 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10455880 99445083 PMID: 10517495
Natural killer cell cytotoxicity of breast cancer targets is enhanced by two distinct mechanisms of antibody-dependent cellular cytotoxicity against LFA-3 and HER2/**neu**.
Cooley S; Burns L J; Repka T; Miller J S
Department of Medicine, University of Minnesota Cancer Center, Minneapolis 55455, USA.
Experimental hematology (NETHERLANDS) Oct 1999, 27 (10) p1533-41, ISSN 0301-472X Journal Code: 0402313
Contract/Grant No.: PO1-CA-65493; CA; NCI
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
Treatment of advanced breast cancer with autologous stem cell transplantation is limited by a high probability of disease relapse. In clinical trials, interleukin 2 (IL-2) alone can expand natural killer (NK) cells in vivo and increase their cytotoxic activity against breast cancer cell lines, but this increase is modest. Understanding the mechanisms that mediate NK cell lysis of breast cancer targets may lead to improvements of current immunotherapy strategies. NK cells from normal donors or patients receiving subcutaneous IL-2 were tested in cytotoxicity assays against five breast cancer cell lines. The role of adhesion molecules and antibodies that interact through Fc receptors on NK cells was explored. NK cell lysis of breast cancer targets is variable and is partially dependent on recognition through ICAM-1 and CD18. While blocking CD2 slightly decreased cytotoxicity, contrary to expectations, an antibody against CD58 (the ligand for CD2), failed to block killing and instead mediated an increased cytotoxicity that correlated with target density of CD58. The CD58 antibody-enhanced killing was dependent not only on FcRgammaIII but also on CD2 and ICAM-1/CD18. To further elucidate the mechanism of this CD58 antibody-dependent cellular cytotoxicity (ADCC), another antibody was tested. Trastuzumab (Herceptin), a humanized antibody against HER2/**neu**, mediated potent ADCC against all the HER2/**neu** positive breast cancer targets. Unlike CD58 antibody-mediated ADCC, Herceptin ADCC was minimally affected by blocking antibodies to CD2 or ICAM-1/CD18, which suggests a different mechanism of action. This study shows that multiple mechanisms are involved in NK cell lysis of breast cancer targets, that none of the targets are inherently **resistant** to killing, and that two distinct mechanisms of ADCC can target immunotherapy to breast cancer cells.

6/3,AB/73 (Item 73 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10392323 99384857 PMID: 10455915
Synergistic antitumor effects of HER2/**neu** antisense oligodeoxynucleotides and conventional chemotherapeutic agents.
Roh H; Hirose C B; Boswell C B; Pippin J A; Drebin J A
Department of Surgery, Washington University School of Medicine, St Louis, MO 63110, USA.
Surgery (UNITED STATES) Aug 1999, 126 (2) p413-21, ISSN 0039-6060 Journal Code: 0417347
Contract/Grant No.: T32CA09621; CA; NCI
Document type: Journal Article
Languages: ENGLISH

Main Citation Owner: NLM
Record type: Completed
BACKGROUND: The HER2/**neu** oncogene is overexpressed in a substantial fraction of human tumors. HER2/**neu** overexpressing tumors may be intrinsically **resistant** to chemotherapy. The present study examined the ability of antisense-mediated downregulation of HER2/**neu** expression to enhance the antitumor effects of conventional chemotherapeutic agents against human tumor cells that overexpress HER2/**neu**. METHODS: The effects of HER2/**neu** antisense oligodeoxynucleotides (ODNs) on the growth inhibitory and proapoptotic activity of several distinct chemotherapeutic agents were examined in vitro. In vivo effects of HER2/**neu** antisense ODNs in combination with doxorubicin hydrochloride were assessed by examining the growth of human tumor xenografts implanted into nude mice. RESULTS: The proliferation of tumor cell lines that overexpress HER2/**neu** was inhibited by antisense ODNs in combination with conventional chemotherapeutic agents in an additive or synergistic fashion. Such combination therapy also demonstrated synergistic activation of apoptosis. HER2/**neu** antisense ODNs in combination with doxorubicin hydrochloride demonstrated synergistic antitumor effects in vivo as well. CONCLUSIONS: Downregulation of HER2/**neu** expression can enhance the sensitivity of human cancer cells, which overexpress HER2/**neu** to the cytotoxic effects of chemotherapy. Antisense ODNs targeting the HER2/**neu** gene may play a role in cancer therapy.

6/3,AB/74 (Item 74 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10353306 99350708 PMID: 10419854
Novel anticancer **drug** discovery.
Buolamwini J K
Department of Medicinal Chemistry, Research Institute of Pharmaceutical Sciences, School of Pharmacy, University of Mississippi, MS 38677, USA. mcjkb@olemiss.edu
Current opinion in chemical biology (ENGLAND) Aug 1999, 3 (4) p500-9 , ISSN 1367-5931 Journal Code: 9811312
Document type: Journal Article; Review; Review, Tutorial
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
There is at present, much optimism about the possibility of finding selective anticancer drugs that will eliminate the cytotoxic side effects associated with conventional cancer chemotherapy. This hope is based on uncovering many novel molecular targets that are 'cancer-specific', which will allow the targeting of cancer cells while normal cells are spared. Thus far, encouraging results have been obtained with several of these novel agents at the preclinical level, and clinical trials have begun. These targets are involved at one level or more in tumor biology, including tumor cell proliferation, angiogenesis and metastasis. Novel targets for which advances are being made include the following: growth factor receptor tyrosine kinases such as the epidermal growth factor receptor and **HER -2/neu** (proliferation); the vascular endothelial growth factor receptor and the basic fibroblast growth factor receptor (angiogenesis); the oncogenic GTP-binding protein Ras (especially agents targeting Ras farnesylation, farnesyltransferase inhibitors) (proliferation); protein kinase C (proliferation and **drug resistance**); cyclin-dependent kinases (proliferation); and matrix metalloproteinases and angiogenin (angiogenesis and metastasis). Less explored, but potentially useful targets include the receptor tyrosine kinase platelet-derived growth factor receptor, mitogen-activated protein kinase cascade oncogenes such as Raf-1 and mitogen-activated protein kinase kinase, cell adhesion molecules such as integrins, anti-apoptosis proteins such as Bcl-2, MDM2 and survivin, and the cell life-span target telomerase.

6/3,AB/75 (Item 75 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10333993 99323396 PMID: 10397267
Contribution of c-erbB-2 and topoisomerase IIalpha to chemoresistance in ovarian cancer.
Hengstler J G; Lange J; Kett A; Dornhofer N; Meinert R; Arand M; Knapstein P G; Becker R; Oesch F; Tanner B
Institute of Toxicology, University of Mainz, Germany. hengstle@mail.Uni-Mainz.de
Cancer research (UNITED STATES) Jul 1 1999, 59 (13) p3206-14, ISSN 0008-5472 Journal Code: 2984705R
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
Overexpression of the c-erbB-2 (**HER-2/neu**) oncogene, which encodes a transmembrane receptor tyrosine kinase, has been shown to be associated with poor prognosis in ovarian and breast cancer. Recent studies indicate that c-erbB-2 may also be involved in determining the chemosensitivity of human cancers. In the present study, we examined the role of c-erbB-2 for chemoresistance in ovarian cancer. Overexpression of c-erbB-2 mRNA in tumor tissue was associated with a shorter survival of patients with primary ovarian cancer (P = 0.0001; n = 77) and was an independent prognostic factor in the proportional-hazard model adjusted for International Federation of Gynecologists and Obstetricians stage, residual disease, chemotherapy, and age (P = 0.035). A significant association between expression of c-erbB-2 mRNA and survival was obtained for the subgroup of patients who received a standard chemotherapy with carboplatin or cisplatin and cyclophosphamide (P = 0.0003), whereas only a nonsignificant trend was observed for patients who did not receive a standard chemotherapy (P = 0.124). In addition, the application of a standard chemotherapy improved the survival of patients with relatively low c-erbB-2 expression (P = 0.013) but not of patients with overexpression of c-erbB-2 (P = 0.359). Expression of c-erbB-2 mRNA correlated with expression of topoisomerase IIalpha mRNA determined by a reverse semiquantitative PCR technique (P = 0.009), whereas expression of c-erbB-2 and topoisomerase IIbeta mRNA did not correlate (P = 0.221). To examine the hypothesis that coamplified and/or coregulated topoisomerase IIalpha contributes to the **resistance** of c-erbB-2-overexpressing carcinomas, we established a chemosensitivity assay using primary cells from an ovarian carcinoma that overexpressed both c-erbB-2 and topoisomerase IIalpha. The combination of carboplatin with nontoxic concentrations of the topoisomerase II inhibitors etoposide or novobiocin enhanced the toxicity of carboplatin. In contrast, the tyrosine kinase inhibitor emodin exhibited no chemosensitizing effect in cells of this individual carcinoma. In conclusion, overexpression of c-erbB-2 was associated with poor prognosis and poor response to chemotherapy. The data suggest that topoisomerase IIalpha, which correlates with c-erbB-2 expression, contributes to the **resistance** of c-erbB-2-overexpressing carcinomas.

6/3,AB/76 (Item 76 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10284200 99262335 PMID: 10328849
A metastatic breast tumor cell line, GI-101A, is estrogen receptor positive and responsive to estrogen but **resistant** to tamoxifen.
Morrissey J J; Raney S
Motorola Biological Research Program, Ft. Lauderdale, FL 33322, USA.
Cell biology international (ENGLAND) 1998, 22 (6) p413-9, ISSN 1065-6995 Journal Code: 9307129

Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed

The progression of human breast cancer is often associated with a loss of estrogen dependence for growth, a **resistance** to estrogen antagonists such as tamoxifen, and the metastatic spread of the disease to secondary sites. Cell lines developed from such advanced breast tumors are often metastatic in athymic mice, show a loss of estrogen receptor mRNA and protein (ER-), and do not respond to 17beta-estradiol. However many advanced human breast tumors do express significant amounts of ER transcript, especially when analyzed by more sensitive methods of detection including RT-PCR and Ribonuclease Protection Assay (RPA). No metastatic, ER+breast tumor cell line has previously existed to examine the role of ER in metastatic progression and acquired **drug** (tamoxifen) **resistance** . The GI-101A cell line was recently developed from a metastatic breast tumor xenograft and is both tumorogenic and metastatic to the lungs and lymph node when injected into athymic mice, a pattern similar to that seen in patients. While Western blot analysis initially indicated that GI-101A was ER-, analysis of ER mRNA by RT-PCR and RPA have demonstrated the expression of ER (as well as EGF receptor and **neu** oncogene) transcripts. Functional ER in GI-101A was confirmed by a clear growth response to 17beta-estradiol in culture. Optimal 17beta-estradiol concentrations were significantly lower for GI101A than for MCF-7 (1 n m as opposed to >/=10 n m), and GI-101A growth was inhibited at 17beta-estradiol concentrations above 10 n m. Unlike MCF-7 cells, GI-101A shows constitutive expression of pS2 protein in hormone depleted media with no apparent induction by 17beta-estradiol supplimentation, as well as a **resistance** to the anti-estrogen tamoxifen at concentrations up to 10 n m. Finally, ER transcripts which likely represent an alternately spliced ER variant which has previously been shown to encode a constitutively active ER protein have been detected in GI-101A at levels similar to the wild type transcript, and offer a possible mechanism for estrogen independence, tamoxifen **resistance**, and constitutive pS2 expression.
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6/3,AB/77 (Item 77 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10262697 99254312 PMID: 10321009
[Pneumonia: what's new?]
Pneumonie: Was ist **neu**?
Tauber M G
Institut fur Medizinische Mikrobiologie, Universitat Bern. taeuber@imm.unibe.ch
Schweizerische medizinische Wochenschrift (SWITZERLAND) Apr 10 1999, 129 (14) p563-9, ISSN 0036-7672 Journal Code: 0404401
Document type: Journal Article; Review; Review, Tutorial ; English Abstract
Languages: GERMAN
Main Citation Owner: NLM
Record type: Completed

Pneumonia continues to be one of the most important infectious diseases which often leads to hospital admissions and is occasionally fatal. The spectrum of causative organisms, their sensitivity pattern to antibiotics, diagnostic tools, and available antibiotics are continually changing. Currently, the most disquieting trend is the increasing development of **resistance** to commonly used antibiotics by the pneumococcus. Although this trend has thus far been observed primarily in other countries, it will most likely not spare Switzerland. Rational empiric therapy must include careful clinical assessment of the patient, knowledge of the spectrum of organisms locally causing pneumonias, including their **resistance** patterns, as well as a prognostic assessment of the patient. Using these

factors, possible antibiotic schemes for empiric therapy of community-acquired pneumonia are reviewed.

6/3,AB/78 (Item 78 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10255984 99245903 PMID: 10230872
The immunology and immunotherapy of breast cancer: an update.
Hadden J W
University of South Florida College of Medicine, Department of Internal Medicine, Tampa, USA.
International journal of immunopharmacology (ENGLAND) Feb 1999, 21 (2) p79-101, ISSN 0192-0561 Journal Code: 7904799
Document type: Journal Article; Review; Review, Tutorial
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
Adenocarcinomas of the breast behave clinically and epidemiologically in ways that show host **resistance** factors are important for outcome in addition to grade and stage of malignancy. Immune reactivity to autologous tumors is indicated by the general presence of lymphoid infiltration (LI) and regional lymph node changes; however, these changes predict favorable outcome only in non-metastatic disease. LI is characterized by CD4+ and CD8+ tumor infiltrating lymphocytes reflecting latent cell-mediated immunity (CMI). CMI and humoral immune reactivity have been demonstrated to autologous tumor and a variety of tumor-associated antigens (TAA) have been implicated including CEA, **HER-2/neu**, MAGE-1, p53, T/Tn and MUC-1. Immune incompetence involving CMI is progressive with the stage of breast cancer and is prognostically significant. Immunotherapy of several types has been designed to address this immunodeficiency and the TAAs involved. Animal models have employed **drug** therapy, cytokine transfection, vaccines with autologous tumor, cytokines like interferon alpha (IFN-alpha) and interleukin-2 (IL-2), TAA tumor vaccines, and immunotoxins with evidence of tumor regression by immunologic means. Immunotherapy of human breast cancer is a rapidly growing experimental area. Positive results have been obtained with natural IFN and interleukins, particularly in combination strategies (but not with high dose recombinant IFN or IL-2), with autologous tumor vaccine (but not yet with transfected autologous tumor); with a mucin carbohydrate vaccine (Theratope) in a combination strategy (but not with mucin core antigen) and with several immunotoxins. Combination strategies involving immunorestoration, contrasuppression, adjuvant, and immunotoxins are suggested for the future.

6/3,AB/79 (Item 79 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10211673 99202780 PMID: 10188897
Stage III and oestrogen receptor negativity are associated with poor prognosis after adjuvant high-dose therapy in high-risk breast cancer.
Hohaus S; Funk L; Martin S; Schlenk R F; Abdallah A; Hahn U; Egerer G; Goldschmidt H; Schneeweiss A; Fersis N; Kaul S; Wallwiener D; Bastert G; Haas R
Department of Internal Medicine V, University of Heidelberg, Germany.
British journal of cancer (SCOTLAND) Mar 1999, 79 (9-10) p1500-7, ISSN 0007-0920 Journal Code: 0370635
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
We report on the efficacy and toxicity of a sequential high-dose therapy with peripheral blood stem cell (PBSC) support in 85 patients with

high-risk stage II/III breast cancer. There were 71 patients with more than nine tumour-positive axillary lymph nodes. An induction therapy of two cycles of ifosfamide (total dose, 7.5 g m(-2)) and epirubicin (120 mg m(-2)) was given, and PBSC were harvested during G-CSF-supported leucocyte recovery following the second cycle. The PBSC-supported high-dose chemotherapy consisted of two cycles of ifosfamide (total dose, 12,000 mg m(-2)), carboplatin (900 mg m(-2)) and epirubicin (180 mg m(-2)). Patients were autografted with a median number of 3.7 x 10(6) CD34+ cells kg(-1) (range, 1.9-26.5 x 10(6)) resulting in haematological reconstitution within approximately 2 weeks following high-dose therapy. The toxicity was moderate in general, and there was no treatment-related toxic death. Twenty-one patients relapsed between 3 and 30 months following the last cycle of high-dose therapy (median, 11 months). The probability of disease-free and overall survival at 4 years were 60% and 83%, respectively. According to a multivariate analysis, patients with stage II disease had a significantly better probability of disease-free survival (74%) in comparison to patients with stage III disease (36%). The probability of disease-free survival was also significantly better for patients with oestrogen receptor-positive tumours (70%) compared to patients with receptor-negative ones (40%). Bone marrow samples collected from 52 patients after high-dose therapy were examined to evaluate the prognostic relevance of isolated tumour cells. The proportion of patients presenting with tumour cell-positive samples did not change in comparison to that observed before high-dose therapy (65% vs 71%), but a decrease in the incidence and concentration of tumour cells was observed over time after high-dose therapy. This finding was true for patients with relapse and for those in remission, which argues against a prognostic significance of isolated tumour cells in bone marrow. In conclusion, sequential high-dose chemotherapy with PBSC support can be safely administered to patients with high-risk stage II/III breast cancer. Further intensification of the therapy, including the addition of non-cross **resistant** drugs or immunological approaches such as the use of antibodies against **HER -2/NEU** , may be envisaged for patients with stage III disease and hormone receptor-negative tumours.

6/3,AB/80 (Item 80 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10186273 99193907 PMID: 10096243
c-erbB-2 (**HER-2/neu**) protein and **drug resistance** in breast cancer patients treated with induction chemotherapy.
Vargas-Roig L M; Gago F E; Tello O; Martin de Civetta M T; Ciocca D R
Laboratory of Reproduction and Lactaction, Regional Center for Scientific and Technological Research, Mendoza, Argentina.
International journal of cancer. Journal international du cancer (UNITED STATES) Apr 20 1999, 84 (2) p129-34, ISSN 0020-7136 Journal Code: 0042124
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
Expression of c-erbB-2 protein has been associated with poor prognosis and poor response to chemotherapy in breast cancer patients. In the present prospective study, we have analyzed whether c-erbB-2, p53 and P170 proteins may be determinants of tumor **resistance** in locally advanced breast cancer patients treated with induction chemotherapy. Biopsies (n = 60) were examined by immuno-histochemistry; in 62% of cases core or incisional biopsies were taken before **drug** administration, allowing comparison in paired biopsies of the cytological and molecular changes induced by treatment Sixty percent of the patients received relatively high doses of FAC or FEC (5-fluorouracil, doxorubicin or epirubicin and cyclophosphamide), and 40% received relatively high doses of doxorubicin or

epirubicin alone. No significant changes were observed in the molecular markers studied following chemotherapy; in the few biopsies where changes appeared, the changes did not exhibit any significant or similar trend. For 30 of the patients who received FAC/FEC treatment, follow-up reached a median of 34 months. In these cases, neither the clinical (reduction in tumor size) nor the histological (evaluated after neoadjuvant chemotherapy) responses showed statistically significant differences between the patients who developed distant metastases and the disease-free patients. c-erbB-2 was over-expressed in 50% of patients who developed distant metastases vs. 7% of the disease-free patients. Disease free survival (DFS) curves between c-erbB-2-positive and c-erbB-2-negative patients were statistically significant. No correlation between p53 or P170 expression with DFS was found. Our results suggest that c-erbB-2 protein expression is associated with development of distant metastases in breast cancer patients treated with relatively high doses of anthracyclines in induction chemotherapy.

6/3,AB/81 (Item 81 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10173474 99163956 PMID: 10066073
HER-2/neu as a predictive marker of response to breast cancer therapy.
Pegram M D; Pauletti G; Slamon D J
Department of Medicine, University of California Los Angeles School of Medicine, 90095, USA.
Breast cancer research and treatment (NETHERLANDS) 1998, 52 (1-3) p65-77, ISSN 0167-6806 Journal Code: 8111104
Document type: Journal Article; Review; Review, Tutorial
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
Amplification of the **HER-2/neu** (c-erbB-2) gene resulting in overexpression of the p185HER-2 growth factor receptor occurs in approximately 25% of early stage breast cancers. **HER-2/neu** has been established as an important independent prognostic factor in early stage breast cancer in large cohorts of patients and in cohorts with very long (30 year) follow-up duration. New data are emerging to suggest that **HER-2/neu** may be useful not only as a prognostic factor but also as a predictive marker for projecting response to chemotherapeutics, antiestrogens, and therapeutic anti-**HER-2/neu** monoclonal antibodies. In this review we highlight recent data on **HER-2/neu** as a predictive marker of response to breast cancer therapy and discuss the clinical implications of this information. The difficulty in comparing results from different data sets due to the wide variety of reagents and technologies used to detect **HER-2/neu** amplification/overexpression in clinical specimens is also discussed. Finally, we report results from experimental models of **HER-2/neu** overexpression which have been used in an effort to understand the relationship between **HER-2/neu** and response to chemotherapeutics and antiestrogens in breast cancer.

6/3,AB/82 (Item 82 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10132843 99111150 PMID: 9815592
Adenovirus E1A expression enhances the sensitivity of an ovarian cancer cell line to multiple cytotoxic agents through an apoptotic mechanism.
Brader K R; Wolf J K; Hung M C; Yu D; Crispens M A; van Golen K L; Price J E
Departments of Cell Biology, The University of Texas M.D. Anderson Cancer Center, Houston, Texas 77030, USA.
Clinical cancer research : an official journal of the American

Association for Cancer Research (UNITED STATES) Nov 1997, 3 (11) p2017-24, ISSN 1078-0432 Journal Code: 9502500
Contract/Grant No.: CA51053; CA; NCI
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed

The introduction of adenovirus 5 E1A into the SKOV3ip1 ovarian cancer cell line was shown previously to suppress HER2/**neu** expression and reduce the malignant potential of these cells (Yu et al., Cancer Res., 53: 891-898, 1993). In this report, we show that reduction of p185 in cells stably expressing E1A protein was coincident with increased sensitivity to cytotoxic agents. The LD50 of cisplatin was reduced 6-fold, and the LD50 of paclitaxel and doxorubicin was reduced 10-fold in E1A-expressing cells compared with control cells. The growth of SKOV3ip1 and control cells was unchanged in the presence of 150 ng/ml of tumor necrosis factor-alpha, whereas the growth of E1A-expressing cells was reduced by 30 to 40%. When we used a physiologically obtainable concentration of paclitaxel (0.5 microM), DNA laddering consistent with apoptotic cell death was seen after a 24-h exposure in the E1A-expressing cells, whereas laddering and DNA fragmentation were only detected in DNA from control cells after longer exposure (48 h) at a 20-fold higher concentration of paclitaxel. The SKOV3ip1 cells do not express p53 protein; hence, the induction of apoptosis by paclitaxel is through a p53-independent pathway. Despite their diverse mechanisms of action, the cytotoxic effects of cisplatin, doxorubicin, paclitaxel, and tumor necrosis factor-alpha were enhanced by the expression of E1A proteins in the SKOV3ip1 ovarian cancer cells. This suggests that these agents share a common final pathway of cell killing, which may represent a potential therapeutic target in **resistant** ovarian cancers.

6/3,AB/83 (Item 83 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10033375 99011385 PMID: 9792896
Novel approaches in development for the treatment of pancreatic cancer.
Butera J; Malachovsky M; Rathore R; Safran H
Department of Medicine, Brown University, Providence Rhode Island, USA.
Frontiers in bioscience computer file : a journal and virtual library (UNITED STATES) Nov 1 1998, 3 pE226-9, ISSN 1093-4715 Journal Code: 9702166
Document type: Journal Article; Review; Review, Tutorial
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed

Pancreatic adenocarcinomas are among the most **resistant** neoplasms to conventional chemotherapeutics. This has prompted intense investigations of novel non-cytotoxic agents based on new understandings of the molecular pathobiology of human malignancies. This review will focus on the potential uses of three new classes of agents: farnesyl transferase (FTPase) inhibitors, matrix metalloproteinase inhibitors (MMPI's) and antibodies to the **HER-2/neu** oncogene. When used as single agents, FTPase inhibitors and MMPI's may be cytostatic, helping to delay the growth of these cancers. All three classes of agents may have the greatest benefit when used in conjunction with traditional anticancer modalities. The biology of these agents will reviewed.

6/3,AB/84 (Item 84 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10033268 99025850 PMID: 9809978
Increased sensitivity of adriamycin-selected tumor lines to CTL-mediated

lysis results in enhanced **drug** sensitivity.
Fisk B; Ioannides C G
Department of Gynecologic Oncology, The University of Texas M. D. Anderson Cancer Center, and The University of Texas Medical School-Houston, 77030, USA.
Cancer research (UNITED STATES) Nov 1 1998, 58 (21) p4790-3, ISSN 0008-5472 Journal Code: 2984705R
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
The emergence of **drug resistance** to chemotherapeutic agents is a major cause of treatment failure in cancer therapy. Therefore, much effort has been aimed at circumventing or reversing this undesired effect. Recently, we found that tumor cell lines selected for their multidrug-**resistant** phenotype can also exhibit increased levels of TAP mRNA and MHC class I proteins. This raised the question of whether **drug**-**resistant** tumors are more readily recognized by MHC-restricted CTLs. In this report, we show that five of five MHC class I+ tumor cell lines grown in medium containing Adriamycin developed into variants that expressed higher levels of MHC class I than did their corresponding parental cell lines. This was not observed with a MHC class I- cell line. No similar association was noted for changes in the expression of either **HER-2** or intercellular adhesion molecule 1 protein. We also found that MHC class I+ **drug**-selected variants were more readily lysed by MHC-restricted, tumor-associated CTLs than were the **drug**-sensitive parental cell lines. When the **drug**-selected variants were cocultured with the same CTLs to eliminate tumor cells expressing higher levels of MHC-I (MHC-Ihi), the CTL-**resistant** tumor cells exhibited a **drug** sensitivity profile similar to that of the parental cell lines that were not exposed to Adriamycin. These findings suggest that certain chemotherapeutic drugs may increase the immunogenicity of some tumors, and that CTL immunotherapy may help reverse **drug resistance**.

6/3,AB/85 (Item 85 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10004955 98445624 PMID: 9772447
The reversion of multidrug **resistance** in tumour cell line MCF-7/Adr by ribozyme]
Yuan Y; Zhang J; Zhou D
Department of Cancer Second Hospital First Military Medical University, Guang Zhou.
Zhonghua yi xue za zhi (CHINA) Jul 1997, 77 (7) p494-6, ISSN 0376-2491 Journal Code: 7511141
Document type: Journal Article ; English Abstract
Languages: CHINESE
Main Citation Owner: NLM
Record type: Completed
OBJECTIVE: To construct a specific hammerhead ribozyme possessing catalytic activity that cleaves the mdr1 mRNA for reversing the **resistant** phenotype in tumour cell line. METHODS: A DNA sequence encoding the ribozyme gene was incorporated into a eukaryotic expression vector (pH beta Apr-1 **neu**) and transfected into the human breast carcinoma cell line MCF-7/Adr, which is **resistant** to adriamycin and expresses the MDR phenotype. RESULTS: The ribozyme was stably expressed in the cell line, and decreased the level of mdr1 mRNA expression by 83.5%. The ribozyme inhibited the formation of P-glycoprotein and reduced the cell's **resistance** to adriamycin. CONCLUSION: The **resistant** cells were 1,000-fold more **resistant** than the parental cell line (MCF-7), whereas those cell clones that showed ribozyme expression were only 6-fold more **resistant** than the parental cell line.

6/3,AB/86 (Item 86 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09921719 98368414 PMID: 9704716
Phase II study of receptor-enhanced chemosensitivity using recombinant humanized anti-p185HER2/**neu** monoclonal antibody plus cisplatin in patients with HER2/**neu** -overexpressing metastatic breast cancer refractory to chemotherapy treatment.
Pegram M D; Lipton A; Hayes D F; Weber B L; Baselga J M; Tripathy D; Baly D; Baughman S A; Twaddell T; Glaspy J A; Slamon D J
Department of Medical Oncology, The University of California at Los Angeles, USA. mpegram@ucla.edu
Journal of clinical oncology : official journal of the American Society of Clinical Oncology (UNITED STATES) Aug 1998, 16 (8) p2659-71, ISSN 0732-183X Journal Code: 8309333
Contract/Grant No.: 1K12CA01714; CA; NCI
Document type: Clinical Trial; Clinical Trial, Phase II; Journal Article; Multicenter Study
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
PURPOSE: To determine the toxicity, pharmacokinetics, response rate, and response duration of intravenous (i.v.) administration of recombinant, humanized anti-p185HER2 monoclonal antibody (rhuMAb HER2) plus cisplatin (CDDP) in a phase II, open-label, multicenter clinical trial for patients with HER2/**neu** -overexpressing metastatic breast cancer. PATIENTS AND METHODS: The study population consisted of extensively pretreated advanced breast cancer patients with HER2/**neu** overexpression and disease progression during standard chemotherapy. Patients received a loading dose of rhuMAb HER2 (250 mg i.v.) on day 0, followed by weekly doses of 100 mg i.v. for 9 weeks. Patients received CDDP (75 mg/m2) on days 1, 29, and 57. RESULTS: Of 37 patients assessable for response, nine (24.3%) achieved a PR, nine (24.3%) had a minor response or stable disease, and disease progression occurred in 19 (51.3%). The median response duration was 5.3 months (range, 1.6-18). Grade III or IV toxicity was observed in 22 of 39 patients (56%). The toxicity profile reflected that expected from CDDP alone with the most common toxicities being cytopenias (n = 10), nausea/vomiting (n = 9), and asthenia (n = 5). Mean pharmacokinetic parameters of rhuMAb HER2 were unaltered by coadministration of CDDP. CONCLUSION: The use of rhuMAb HER2 in combination with CDDP in patients with HER2/**neu** -overexpressing metastatic breast cancer results in objective clinical response rates higher than those reported previously for CDDP alone, or rhuMAb HER2 alone. In addition, the combination results in no apparent increase in toxicity. Finally, the pharmacology of rhuMAb HER2 was unaffected by coadministration with CDDP.

6/3,AB/87 (Item 87 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09856861 98295608 PMID: 9633851
Biological therapy of ovarian cancer: current directions.
Bookman M A
Department of Medical Oncology, Fox Chase Cancer Center, Philadelphia, PA 19111, USA.
Seminars in oncology (UNITED STATES) Jun 1998, 25 (3) p381-96, ISSN 0093-7754 Journal Code: 0420432
Document type: Journal Article; Review; Review, Academic
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
Despite recent advances in the chemotherapy of ovarian cancer, the development of alternative therapies that retain activity against

drug-resistant tumors remains a high priority. Our knowledge regarding growth factors, cytokines, and the immune response continues to expand, and molecular biology has provided an increased diversity of reagents for clinical evaluation. This review focuses on regulatory targets in ovarian cancer, including Her2/**neu** (c-erbB2) and other growth factor receptors; interferons, interleukins, and other immunoregulatory cytokines; cellular adhesion molecules; antigen-specific T lymphocytes and adoptive immunotherapy; choice of monoclonal antibody reagents and advances in antibody engineering, including recombinant single-chain binding sites, chimeric proteins, radioconjugates, cytotoxic **drug** conjugates, immunotoxins, and bispecific antibodies. Although specific roles for biologic therapy in the management of ovarian cancer have yet to be defined, current priorities for clinical research are reviewed.

6/3,AB/88 (Item 88 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09740431 98177590 PMID: 9516946
HER-2 expression and response to tamoxifen in estrogen receptor-positive breast cancer: a Southwest Oncology Group Study.
Elledge R M; Green S; Ciocca D; Pugh R; Allred D C; Clark G M; Hill J; Ravdin P; O'Sullivan J; Martino S; Osborne C K
University of Texas Health Science Center, San Antonio 78284-7884, USA.
Clinical cancer research : an official journal of the American Association for Cancer Research (UNITED STATES) Jan 1998, 4 (1) p7-12, ISSN 1078-0432 Journal Code: 9502500
Contract/Grant No.: CA22433; CA; NCI; CA32102; CA; NCI; CA37429; CA; NCI; +
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
HER-2/neu is a growth factor receptor, the expression of which has been associated with a more aggressive breast tumor biology and **resistance** to some types of chemotherapy. Preliminary laboratory and clinical data have led to claims that **HER-2/neu** expression is also associated with **resistance** to tamoxifen. Therefore, to test the hypothesis that **HER-2/neu** expression is associated with a poorer response to tamoxifen, a shorter time to treatment failure (TTF), and worse survival in estrogen receptor (ER)-positive metastatic breast cancer, we examined 205 paraffin-embedded blocks of tumors from patients enrolled on Southwest Oncology Group 8228 for **HER-2/neu** expression. Tumors were ER positive (ER level > 3 fmol/mg cytosolic protein in either primary tumors or metastases), and patients had not received any prior therapy for metastatic disease. All patients were treated with daily tamoxifen. The study began in 1982, and median follow-up of patients who are still alive is now 9 years. Membrane staining for **HER-2/neu** was evaluated by immunohistochemistry using antibody TAB 250 and was scored according to the proportion of cells staining positive; tumors were deemed positive if > 1% of the cells stained for **HER-2/neu**. **HER-2/neu** positivity was associated with lower ER values (P = 0.04) and low bcl-2 (P = 0.01). **HER-2/neu** positivity was not significantly associated with response rate (negative versus positive, 57 versus 54%; P = 0.67), TTF (median, 8 versus 6 months; P = 0.15), or survival (median, 31 versus 29 months; P = 0.36). There was also no significant evidence of a progressive relationship between an increasing proportion of cells expressing **HER-2/neu** and a shorter TTF or survival. **HER-2/neu** expression in ER-positive metastatic breast cancer is not significantly associated with a poorer response to tamoxifen or a more aggressive clinical course. Earlier suggestions to the contrary may have been due to failure to rigorously exclude ER-negative tumors, which are much less likely to respond to

tamoxifen and more likely to have high **HER-2/neu** levels.

6/3,AB/89 (Item 89 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09645930 98069311 PMID: 9406237
Targeting gene therapy to cancer: a review.
Dachs G U; Dougherty G J; Stratford I J; Chaplin D J
Gray Laboratory, Mount Vernon Hospital, Northwood, UK. dachs@graylab.ac.uk
Oncology research (UNITED STATES) 1997, 9 (6-7) p313-25, ISSN 0965-0407 Journal Code: 9208097
Document type: Journal Article; Review; Review, Tutorial
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed

In recent years the idea of using gene therapy as a modality in the treatment of diseases other than genetically inherited, monogenic disorders has taken root. This is particularly obvious in the field of oncology where currently more than 100 clinical trials have been approved worldwide. This report will summarize some of the exciting progress that has recently been made with respect to both targeting the delivery of potentially therapeutic genes to tumor sites and regulating their expression within the tumor microenvironment. In order to specifically target malignant cells while at the same time sparing normal tissue, cancer gene therapy will need to combine highly selective gene delivery with highly specific gene expression, specific gene product activity, and, possibly, specific **drug** activation. Although the efficient delivery of DNA to tumor sites remains a formidable task, progress has been made in recent years using both viral (retrovirus, adenovirus, adeno-associated virus) and nonviral (liposomes, gene gun, injection) methods. In this report emphasis will be placed on targeted rather than high-efficiency delivery, although those would need to be combined in the future for effective therapy. To date delivery has been targeted to tumor-specific and tissue-specific antigens, such as epithelial growth factor receptor, c-kit receptor, and folate receptor, and these will be described in some detail. To increase specificity and safety of gene therapy further, the expression of the therapeutic gene needs to be tightly controlled within the target tissue. Targeted gene expression has been analyzed using tissue-specific promoters (breast-, prostate-, and melanoma-specific promoters) and disease-specific promoters (carcinoembryonic antigen, **HER-2/neu**, Myc-Max response elements, DF3/MUC). Alternatively, expression could be regulated externally with the use of radiation-induced promoters or tetracycline-responsive elements. Another novel possibility that will be discussed is the regulation of therapeutic gene products by tumor-specific gene splicing. Gene expression could also be targeted at conditions specific to the tumor microenvironment, such as glucose deprivation and hypoxia. We have concentrated on hypoxia-targeted gene expression and this report will discuss our progress in detail. Chronic hypoxia occurs in tissue that is more than 100-200 microns away from a functional blood supply. In solid tumors hypoxia is widespread both because cancer cells are more prolific than the invading endothelial cells that make up the blood vessels and because the newly formed blood supply is disorganized. Measurements of oxygen partial pressure in patients' tumors showed a high percentage of severe hypoxia readings (less than 2.5 mmHg), readings not seen in normal tissue. This is a major problem in the treatment of cancer, because hypoxic cells are **resistant** to radiotherapy and often to chemotherapy. However, severe hypoxia is also a physiological condition specific to tumors, which makes it a potentially exploitable target. We have utilized hypoxia response elements (HRE) derived from the oxygen-regulated phosphoglycerate kinase gene to control gene expression in human tumor cells in vitro and in experimental tumors. The list of genes that have been considered for use in the treatment of cancer is extensive.

It includes cytokines and costimulatory cell surface molecules intended to induce an effective systemic immune response against tumor antigens that would not otherwise develop. Other inventive strategies include the use of internally expressed antibodies to target oncogenic proteins (intrabodies) and the use of antisense technology (antisense oligonucleotides, antigenes, and ribozymes). This report will concentrate more on novel genes encoding prodrug activating enzymes, so-called suicide genes (Herpes simplex virus thymidine kinase, Escherichia coli nitroreductase, E. (ABSTRACT TRUNCATED)

6/3,AB/90 (Item 90 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09614133 98040535 PMID: 9374379
Cisplatin **resistance** is associated with reduced interferon-gamma-sensitivity and increased **HER-2** expression in cultured ovarian carcinoma cells.
Marth C; Widschwendter M; Kaern J; Jorgensen N P; Windbichler G; Zeimet A G; Trope C; Daxenbichler G
Department of Obstetrics and Gynaecology, University Hospital, Innsbruck, Austria.
British journal of cancer (SCOTLAND) 1997, 76 (10) p1328-32, ISSN 0007-0920 Journal Code: 0370635
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
In ovarian carcinoma cells, the combination of interferon-gamma (IFN-gamma) and cisplatin (cDDP) has been reported to result in a synergistic amplification of antiproliferative activity. To assess whether IFN-gamma may also prevent the occurrence of cisplatin **resistance**, the human ovarian carcinoma cell line HTB-77 was treated repeatedly in an intermittent fashion with either cisplatin alone (HTB-77cDDP) or cisplatin plus IFN-gamma (HTB-77cDDP + IFN). After 8 months of treatment, both new lines (HTB-77cDDP or HTB-77cDDP + IFN) were found to be three times more **resistant** to cisplatin than the wild-type cells (HTB-77wt). IFN-gamma could not prevent the development of cisplatin **resistance** . Interestingly, both HTB-77cDDP and HTB-77cDDP + IFN cells were also less IFN-gamma sensitive than the parental line. Both cisplatin-**resistant** lines expressed p185HER-2 and **HER-2** mRNA at a higher concentration than the HTB-77wt cells. IFN-gamma was in all three HTB-77 cell lines able to suppress the **HER-2** message and its encoded protein. The expression of IFN-gamma-induced antigens, namely CA-125 and class II antigens of the major histocompatibility complex (HLA-DR), was markedly augmented by IFN-gamma in all three lines, whereby the most prominent effect was seen in HTB-77cDDP and HTB-77cDDP + IFN.

6/3,AB/91 (Item 91 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09529982 97430052 PMID: 9285690
Chemosensitization of **HER-2/neu**-overexpressing human breast cancer cells to paclitaxel (Taxol) by adenovirus type 5 E1A.
Ueno N T; Yu D; Hung M C
Department of Hematology, The University of Texas M.D. Anderson Cancer Center, Houston 77030, USA.
Oncogene (ENGLAND) Aug 18 1997, 15 (8) p953-60, ISSN 0950-9232 Journal Code: 8711562
Contract/Grant No.: CA58880; CA; NCI; CA60856; CA; NCI
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed

Breast cancer cells that overexpress **HER-2/neu** are more **resistant** to chemotherapeutic agents such as paclitaxel (Taxol) and docetaxel (Taxotere) than those that do not overexpress **HER-2/neu** . In previous work, we showed that the adenovirus type 5 E1A can repress **HER-2/neu** expression at the transcriptional level. Here we first demonstrated that paclitaxel sensitivity correlates with **HER-2/neu** expression level in a panel of mouse fibroblasts expressing different levels of **HER-2/ neu**, and that downregulation of **HER-2/neu** expression by E1A sensitizes the cells to paclitaxel. To further test whether E1A can sensitize **HER-2/neu** -overexpressing human breast cancer cells to paclitaxel through E1A-mediated **HER-2/neu** repression, an adenoviral vector was used to transfer the E1A gene into two human breast cancer cell lines, MDA-MB-453 and MDA-MB-361, that overexpress **HER-2/neu**. After E1A delivery, we observed that **HER -2/neu** expression level was reduced, and cells were treated with paclitaxel. Cell proliferation assays showed a synergistic growth inhibition effect of E1A and paclitaxel. The synergistic effect was also confirmed by soft agar colony-formation assay. Breast cancer cell lines that express low levels of **HER-2/neu**, MDA-MB-435 and MDA-MB-231 cells showed no synergistic growth inhibition effect when treated on the same protocols. Thus, we concluded that the adenovirus type 5 E1A gene can sensitize paclitaxel-**resistant HER-2/ neu**-overexpressing breast cancer cells to the **drug** by repressing **HER-2/neu** expression. This in turn may have important implications for the development of a novel therapy that combines chemotherapy and gene therapy.

6/3,AB/92 (Item 92 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09502703 97412806 PMID: 9267449

A novel synthetic reversible inhibitor of sialidase efficiently blocks secondary but not primary influenza virus infection of MDCK cells in culture.

Barrere B; Driguez P A; Maudrin J; Doutheau A; Aymard M; Quash G
Laboratoire d'Immunochimie, Faculte de Medecine Lyon-Sud, Oullins, France.

Archives of virology (AUSTRIA) 1997, 142 (7) p1365-80, ISSN 0304-8608 Journal Code: 7506870
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed

The sodium salts of 2-difluoromethyl-phenyl-alpha-ketoside of N-acetyl-neuraminic acid (compound 1) and of 4-difluoromethyl-2-methoxy-phe nyl-alpha-ketoside of N-acetylneuraminic acid (compound 2) were designed as potential mechanism-based inhibitors of sialidase. In vitro both of these compounds competitively inhibited the sialidases of Clostridium perfringens and of influenza virus A/HK/1/68. Inhibition was irreversible with the sialidase of Clostridium perfringens whereas it was reversible with that of A/HK/1/68. Compound 2 did not inhibit the hemagglutinin of the virus but exhibited significant anti-influenza activity when added to the medium of Madin-Darby canine kidney (MDCK) cells infected by influenza virus. In non-infected MDCK cells no inhibition of cellular sialidase was observed. Compound 2 did not block primary infection, but inhibited the release of progeny virus from infected cells. Even after 8 passages in its presence, no **resistant** strains were detected. Because of its high Ki (8 x 10(-5) M) compared to the low Ki (1' x 1(-10) M) of 4 guanidino-**Neu** 5 Ac 2en and its reversible inhibition of viral sialidase, its development as an anti-influenza agent is no longer envisaged. Nevertheless, as a mechanism-based irreversible inhibitor of the bacterial enzyme, it could at least be useful for investigating the intrinsic role of sialidase in

infections caused by this strain.

6/3,AB/93 (Item 93 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09476600 97388473 PMID: 9247307
The effect of **HER-2/neu** overexpression on chemotherapeutic **drug** sensitivity in human breast and ovarian cancer cells.
Pegram M D; Finn R S; Arzoo K; Beryt M; Pietras R J; Slamon D J
Division of Hematology-Oncology, University of California at Los Angeles, School of Medicine, 90095, USA.
Oncogene (ENGLAND) Jul 31 1997, 15 (5) p537-47, ISSN 0950-9232 Journal Code: 8711562
Contract/Grant No.: 1K12 CA01714; CA; NCI; R01 CA36827; CA; NCI
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
Recent studies indicate that oncogenes may be involved in determining the sensitivity of human cancers to chemotherapeutic agents. To define the effect of **HER-2/neu** oncogene overexpression on sensitivity to chemotherapeutic drugs, a full-length, human **HER-2/neu** cDNA was introduced into human breast and ovarian cancer cells. In vitro dose-response curves following exposure to 7 different classes of chemotherapeutic agents were compared for **HER-2**- and control-transfected cells. Chemosensitivity was also tested in vivo for **HER-2** - and control-transfected human breast and ovarian cancer xenografts in athymic mice. These studies indicate that **HER-2/neu** overexpression was not sufficient to induce intrinsic, pleomorphic **drug resistance** . Furthermore, changes in chemosensitivity profiles resulting from **HER-2/neu** transfection observed in vitro were cell line specific. In vivo, **HER-2/neu**-overexpressing breast and ovarian cancer xenografts were responsive to different classes of chemotherapeutic drugs compared to control-treated xenografts with no statistically significant differences between **HER-2/neu** -overexpressing and nonoverexpressing xenografts. We found no instance in which **HER-2/neu** -overexpressing xenografts were rendered more sensitive to chemotherapeutic drugs in vivo. **HER-2/neu** -overexpressing xenografts consistently exhibited more rapid regrowth than control xenografts following initial response to chemotherapy suggesting that a high rate of tumor cell proliferation rather than intrinsic **drug resistance** may be responsible for the adverse prognosis associated with **HER-2/neu** overexpression in human cancers.

6/3,AB/94 (Item 94 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09445021 97358724 PMID: 9215820
Prediction of response to antiestrogen therapy in advanced breast cancer patients by pretreatment circulating levels of extracellular domain of the **HER-2**/c-**neu** protein.
Yamauchi H; O'Neill A; Gelman R; Carney W; Tenney D Y; Hosch S; Hayes D F
Lombardi Cancer Center, Department of Medicine, Georgetown University Medical Center, Washington, DC, USA.
Journal of clinical oncology : official journal of the American Society of Clinical Oncology (UNITED STATES) Jul 1997, 15 (7) p2518-25, ISSN 0732-183X Journal Code: 8309333
Contract/Grant No.: CA64057; CA; NCI
Document type: Journal Article
Languages: ENGLISH

Main Citation Owner: NLM
Record type: Completed
PURPOSE: Overexpression of the **HER-2/c-neu** /c-erbB2 proto-oncogene is associated with a worse prognosis in patients with breast cancer, perhaps due to an association of the **HER-2** proto-oncogene protein with **resistance** to hormone and/or chemotherapy. Circulating levels of the extracellular domain (ECD) of the **HER-2/c-neu** -related protein (NRP) are elevated in 20% to 40% of patients with metastatic breast cancer. We investigated whether pretreatment levels of NRP predict response to hormone therapy (HT). MATERIALS AND METHODS: Circulating NRP levels were determined in 94 patients who participated in a randomized trial of three different doses of the antiestrogen, droloxifene (DRO), as first-line HT for metastatic breast cancer. RESULTS: NRP levels were elevated (> or = 5,000 U/mL) in 32 of 94 patients (34%). Only three of 32 patients (9%) with elevated NRP levels responded to DRO, compared with 35 of 62 (56%) with nonelevated NRP levels (P = .00001). Low pretreatment NRP level was the most powerful predictor of response to DRO (odds ratio of response, 22.4; P = .0001). Elevated pretreatment NRP levels were also associated with a shorter time to progression (TTP) and survival duration. CONCLUSION: Pretreatment circulating NRP levels predict a low likelihood of benefit from HT, specifically DRO, in patients with estrogen receptor (ER)-positive and/or progesterone receptor (PgR)-positive or receptor-unknown metastatic breast cancer, even when adjusted for other known predictive factors, such as ER and/or PgR levels, site of disease, disease-free interval from primary treatment to recurrence, and prior adjuvant chemotherapy. These data suggest that pretreatment NRP levels may be useful in deciding whether to treat a patient who otherwise appears to be likely to respond to HT.

6/3,AB/95 (Item 95 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09387816 97279934 PMID: 9134308
Estrogen action in human ovarian cancer.
Clinton G M; Hua W
Department of Biochemistry and Molecular Biology, Oregon Health Sciences University, Portland 97201-3098, USA.
Critical reviews in oncology/hematology (IRELAND) Jan 1997; 25 (1) p1-9, ISSN 1040-8428 Journal Code: 8916049
Document type: Journal Article; Review; Review, Academic
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
Evidence is accumulating for a facilitative role for estrogen in ovarian cancer. Although response to antiestrogen therapy has been poor, there is a distinct subset of patients that respond. Strategies for treatment of ovarian cancer would be improved by identification of patients likely to respond to hormonal therapy. Cell culture models that are responsive or **resistant** to estrogen and antiestrogen may be of value in finding markers that predict responsiveness to hormonal therapy. Several model cell lines have been generated that express ER and proliferate in response to estrogen in vitro. Further studies are needed to better characterize the response of these ER positive cells lines to estrogen in vivo in mouse xenograft models. Expression of many of the same genes are regulated by estrogen in breast and in ovarian cancer cell lines. One exception may be the **HER-2/neu** oncogene product, which is down-regulated by estrogen in responsive breast carcinoma cells but not in two ovarian carcinoma cell lines. Initial analyses of several estrogen responsive and one **resistant** cell model suggests the potential value of progesterone receptor presence and low levels of **HER-2/neu** expression for predicting responsiveness to hormonal therapy. Additional cell models need to be investigated to determine the frequency with which these markers are associated with antiestrogen **resistance**.

6/3,AB/96 (Item 96 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09369814 97245843 PMID: 9090498
Role of oncogenes in **resistance** and killing by cancer therapeutic agents.
el-Deiry W S
Howard Hughes Medical Institute, Department of Medicine, University of Pennsylvania School of Medicine, Philadelphia 19104, USA.
Current opinion in oncology (UNITED STATES) Jan 1997, 9 (1) p79-87, ISSN 1040-8746 Journal Code: 9007265
Document type: Journal Article; Review; Review, Tutorial
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
Chemotherapeutic **drug resistance** is a major clinical problem and cause for failure in the therapy of human cancer. One of the goals of molecular oncology is to identify the underlying mechanisms, with the hope that more effective therapies can be developed. Several mechanisms have been suggested to contribute to chemoresistance: 1) amplification or overexpression of the P-glycoprotein family of membrane transporters (eg, MDR1, MRP, LRP) which decrease the intracellular accumulation of chemotherapy; 2) changes in cellular proteins involved in detoxification (eg, glutathione S-transferase pi, metallothioneins, human MutT homologue, bleomycin hydrolase, dihydrofolate reductase) or activation of the chemotherapeutic drugs (DT-diaphorase, nicotinamide adenine dinucleotide phosphate:cytochrome P-450 reductase); 3) changes in molecules involved in DNA repair (eg, O6-methylguanine-DNA methyltransferase, DNA topoisomerase II, hMLH1, p21WAF1/CIP1; 4) activation of oncogenes such as **Her-2/neu** , bcl-2, bcl-XL, c-myc, ras, c-jun, c-fos, MDM2, p210 BCR-abl, or mutant p53. An overview of these **resistance** mechanisms is presented, with a particular focus on the role of oncogenes. Some current strategies attempting to reverse their effects are discussed.

6/3,AB/97 (Item 97 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09268438 97162177 PMID: 9009164
Effects of the tyrosine-kinase inhibitor geldanamycin on ligand-induced **Her-2/neu** activation, receptor expression and proliferation of **Her-2**-positive malignant cell lines.
Hartmann F; Horak E M; Cho C; Lupu R; Bolen J B; Stetler-Stevenson M A; Pfreundschuh M; Waldmann T A; Horak I D
Metabolism Branch, National Cancer Institute, National Institutes of Health, Bethesda, MD 20892, USA.
International journal of cancer. Journal international du cancer (UNITED STATES) Jan 17 1997, 70 (2) p221-9, ISSN 0020-7136 Journal Code: 0042124
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
Geldanamycin belongs to the family of benzoquinoid ansamycin tyrosine-kinase inhibitors. We have examined its effects on **Her-2/neu** kinase activity, protein expression level, and proliferation of **Her-2** + malignant cells. In SK-BR-3 breast-cancer cells, short-time treatment with geldanamycin completely abrogated gp30-ligand-induced activation of **Her-2** without a change of receptor-expression level. Longer treatment of intact cells with geldanamycin induced decreased steady-state **Her-2** autophosphorylation activity, which correlated with reduction of **Her**

-2 protein expression and phosphotyrosine content of several proteins. The decrease was time- and dose-dependent, starting after 1 hr at 100 nM concentration and reaching completion by 24 hr. The reduction of the **Her-2** protein level probably resulted from increased degradation, since the **Her-2** mRNA level remained constant. Geldanamycin effects were not specific for **Her-2**, since the non-receptor tyrosine-kinase fyn was inhibited equally. In contrast to these results, protein-kinase-C activity was not affected. In 3 other malignant cell lines expressing different amounts of **Her-2** (SK-BR-3 > SK-OV-3 > OVCAR3 > MCF7), geldanamycin also effectively reduced **Her-2**-kinase activity proportionally to the decrease of protein expression. In contrast, in a [3H]-thymidine-uptake assay, cell growth was meaningfully inhibited by geldanamycin at nanomolar concentrations only in SK-BR-3 (IC50 2 nM) and MCF7 (IC50 20 nM), while OVCAR3 was only moderately sensitive (IC50 2 microM) and SK-OV-3 was clearly **resistant** to geldanamycin. In direct comparison with herbimycin A, another benzoquinoid ansamycin that has been more thoroughly characterized, the biologic effects of geldanamycin were more pronounced.

6/3,AB/98 (Item 98 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09267848 97148602 PMID: 9020045
Evidence supporting a signal transduction pathway leading to the radiation-**resistant** phenotype in human tumor cells.
Pirollo K F; Hao Z; Rait A; Ho C W; Chang E H
Department of Surgery, Stanford University Medical Center, California 94305-5328, USA.
Biochemical and biophysical research communications (UNITED STATES) Jan 3 1997, 230 (1) p196-201, ISSN 0006-291X Journal Code: 0372516
Contract/Grant No.: R01 CA45158; CA; NCI
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
A signal transduction pathway, involving oncogenes and their normal counterparts the proto-oncogenes, analogous to that for cell growth and differentiation has been proposed to lead to the phenotype of cellular radioresistance (RR). In this report we provide evidence demonstrating the existence of such a pathway by using antisense oligonucleotides (ASO) to reverse the RR phenotype. Utilizing ASO directed against the raf-1 gene, a central component of this proposed pathway, we were able to reverse the RR phenotype of human tumor cell lines having elevated **HER-2** expression or a mutant form of Ha-ras, two genes upstream of raf-1 in signal transduction. Additionally, anti-ras ASO were able to radiosensitize **HER-2** overexpressing cells. These results, which verify the presence of a signaling pathway leading to cellular RR, also have possible clinical implications for the use of ASO as a means to sensitize radioresistant tumors to radiation therapy.

6/3,AB/99 (Item 1 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
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13961807 BIOSIS NO.: 200200590628
Restoration of estrogen responsiveness by blocking the **HER-2/neu** pathway.
AUTHOR: Witters Lois; Engle Linda; Lipton Allan(a)
AUTHOR ADDRESS: (a)Department of Medicine, Milton S. Hershey Medical Center, 500 University Drive, H046, Hershey, PA, 17033**USA E-Mail: alipton@psu.edu
JOURNAL: Oncology Reports 9 (6):p1163-1166 November-December, 2002

MEDIUM: print
ISSN: 1021-335X
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: **HER-2/neu** gene amplification or protein overexpression is evident in 20-30% of primary breast cancers. Its amplification correlates with poor prognosis. There appears to be an association between **HER-2/neu** overexpression and estrogen independence. The MCF-7 human breast carcinoma cell line is estrogen-dependent and sensitive to the anti-estrogen, tamoxifen (TAM). This line, when transfected with the **HER-2/neu** gene, becomes estrogen-independent and **resistant** to TAM. Blockade of the **HER-2/neu** receptor with 1-5 nM of the humanized **HER-2/neu** antibody, Herceptin, restored estrogen, as well as TAM, sensitivity. These results suggest that Herceptin or similar drugs may restore estrogen sensitivity and the administration of a **HER-2/neu** inhibitor with an anti-estrogen to premenopausal patients should be considered.

2002

6/3,AB/100 (Item 2 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
(c) 2002 BIOSIS. All rts. reserv.

13881030 BIOSIS NO.: 200200509851
Markers and mechanisms of endocrine sensitivity/**resistance**.
AUTHOR: Dowsett Mitch(a)
AUTHOR ADDRESS: (a)Dept. of Biochemistry, Royal Marsden Hospital and Institute of Cancer Research, London, SW3 6JJ**UK
JOURNAL: British Journal of Cancer 86 (Supplement 1):pS4-S5 June, 2002
MEDIUM: print
CONFERENCE/MEETING: British Cancer Research Meeting 2002 Glasgow, UK June 30-July 03, 2002
ISSN: 0007-0920
RECORD TYPE: Citation
LANGUAGE: English
2002

6/3,AB/101 (Item 3 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
(c) 2002 BIOSIS. All rts. reserv.

13826551 BIOSIS NO.: 200200455372
Anti receptor antibodies: Update of their current role in the treatment of breast cancer.
AUTHOR: Piccart M J(a); Mano M(a); Dolci S(a); Di Leo A(a)
AUTHOR ADDRESS: (a)Jules Bordet Institute, Brussels**Belgium
JOURNAL: European Journal of Cancer 38 (Supplement 3):pS88 March, 2002
MEDIUM: print
CONFERENCE/MEETING: 3rd European Breast Cancer Conference Barcelona, Spain March 19-23, 2002
ISSN: 0959-8049
RECORD TYPE: Citation
LANGUAGE: English
2002

6/3,AB/102 (Item 4 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

(c) 2002 BIOSIS. All rts. reserv.

13811533 BIOSIS NO.: 200200440354
Flavopiridol and trastuzumab synergistically inhibit proliferation of breast cancer cells: Association with selective cooperative inhibition of cyclin D1-dependent kinase and Akt signaling pathways.
AUTHOR: Wu Kongming; Wang Chenguang; D'Amico Mark; Lee Richard J; Albanese Chris; Pestell Richard G; Mani Sridhar(a)
AUTHOR ADDRESS: (a)Albert Einstein College of Medicine, 1300 Morris Park Avenue, Chanin 302, Bronx, NY, 10461**USA E-Mail: smani64@aol.com
JOURNAL: Molecular Cancer Therapeutics 1 (9):p695-706 July, 2002
MEDIUM: print
ISSN: 1535-7163
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Cyclin D1 is essential for **Neu**-induced cell growth and is induced by growth factors through Ras-dependent and Ras-independent signaling pathways (1). Because flavopiridol, a novel flavanoid cyclin-cyclin-dependent kinase inhibitor, may function through Ras-dependent and/or -independent pathways, we hypothesized that treatment of breast cancer cells with inhibitors of **Neu** signaling and flavopiridol might synergize to inhibit proliferation. Human breast cancer cell lines, which express high levels of endogenous **Neu** receptor, were treated with the anti-**Neu** antibody, trastuzumab, together with flavopiridol and subject to MTT assay. Cell lines were assayed for alterations in cell cycle by fluorescence-activated cell sorter and signaling proteins by Western blot. Flavopiridol and trastuzumab synergistically inhibited DNA synthesis, cellular proliferation, and contact-dependent growth. Cytotoxic synergy was observed independent of the sequence of addition of the two drugs to cultured cells. In SKBR3 cells, a combination of trastuzumab and flavopiridol inhibited the Ras-MAPK-Akt pathway, decreased cyclin D1 abundance, and kinase activity to a greater extent than either **drug** alone. Compared with single-agent treatment, combination treatment selectively inhibited Akt and pRB phosphorylation. Cytotoxic synergy was observed with flavopiridol plus LY294002 (selective phosphatidylinositol 3-kinase inhibitor) but not with PD98059 (selective mitogen-activated protein kinase kinase 1 inhibitor) suggesting that Akt inhibition may be important in synergy. Zinc-induced overexpression of cyclin D1 in T-47D DELTAMTcycD1 cells were more **resistant** to **drug**-induced cell death when compared with vector-transfected T-47D DELTAMT cells. Cyclin D1 overexpression reverses **drug** treatment induced cell cycle arrest in SKBR3 cells. Flavopiridol and trastuzumab yield cytotoxic synergy in human breast cancer cells overexpressing **Neu**. Cyclin D1 overexpression results in combination **drug resistance**. In addition, inhibition of Akt may prove to be a useful therapeutic strategy in combination with flavopiridol.

2002

6/3,AB/103 (Item 5 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
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13765915 BIOSIS NO.: 200200394736
HER-2/neu and EGFR mRNA expression in tamoxifen **resistant** breast cancer.
AUTHOR: Osipo Clodia(a); Liu Hong; Gajdos Csaba; Jordan V Craig
AUTHOR ADDRESS: (a)Medical School, Robert H. Lurie Comprehensive Cancer Center, Northwestern Univerisity, Chicago, IL**USA
JOURNAL: Proceedings of the American Association for Cancer Research Annual

Meeting 43p318 March, 2002
MEDIUM: print
CONFERENCE/MEETING: 93rd Annual Meeting of the American Association for Cancer Research San Francisco, California, USA April 06-10, 2002
ISSN: 0197-016X
RECORD TYPE: Citation
LANGUAGE: English
2002

 6/3,AB/104   (Item 6 from file: 5)
DIALOG(R)File   5:Biosis Previews(R)
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13757755   BIOSIS NO.: 200200386576
Estrogen regulation of **HER-2/neu** and the development of tamoxifen-stimulated breast cancer.
AUTHOR: Schafer Jennifer MacGregor(a); Badve Sunil(a); Park Woo-Chan(a); Gajdos Csaba(a); Jordan V Craig(a)
AUTHOR ADDRESS: (a)Medical School, R. H. Lurie Comprehensive Cancer Center, Northwestern University, Chicago, IL**USA
JOURNAL: Proceedings of the American Association for Cancer Research Annual Meeting 43p227 March, 2002
MEDIUM: print
CONFERENCE/MEETING: 93rd Annual Meeting of the American Association for Cancer Research San Francisco, California, USA April 06-10, 2002
ISSN: 0197-016X
RECORD TYPE: Citation
LANGUAGE: English
2002

 6/3,AB/105   (Item 7 from file: 5)
DIALOG(R)File   5:Biosis Previews(R)
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13647719   BIOSIS NO.: 200200276540
Clinical course of locally advanced breast cancer (LABC) patients with pathological response to primary concurrent 5-fluorouracil and radiation (FU/RT).
AUTHOR: Formenti S C(a); Cohen D; Tsao-Wei D D; Muggia F M
AUTHOR ADDRESS: (a)Radiation Oncology, New York University School of Medicine, New York, NY**USA
JOURNAL: International Journal of Radiation Oncology Biology Physics 51 (3 Supplement 1):p195-196 2001
MEDIUM: print
CONFERENCE/MEETING: 43rd Annual Meeting of the American Society for Therapeutic Radiology and Oncology San Francisco, CA, USA November 04-08, 2001
ISSN: 0360-3016
RECORD TYPE: Citation
LANGUAGE: English
2001

 6/3,AB/106   (Item 8 from file: 5)
DIALOG(R)File   5:Biosis Previews(R)
(c) 2002 BIOSIS. All rts. reserv.

13562009   BIOSIS NO.: 200200190830
Rational therapeutic intervention in cancer: Kinases as **drug** targets.
AUTHOR: Sawyers Charles L(a)
AUTHOR ADDRESS: (a)Division of Hematology and Oncology, University of California, Los Angeles, 10833 Le Conte Avenue, 11-934 Factor Building,

Los Angeles, CA, 90095-1678**USA E-Mail: csawyers@mednet.ucla.edu
JOURNAL: Current Opinion in Genetics & Development 12 (1):p111-115
February, 2002
MEDIUM: print
ISSN: 0959-437X
DOCUMENT TYPE: Literature Review
RECORD TYPE: Citation
LANGUAGE: English
2002

6/3,AB/107 (Item 9 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
(c) 2002 BIOSIS. All rts. reserv.

13523641 BIOSIS NO.: 200200152462
The ABL-kinase inhibitor STI571 causes BCR-ABL independent **resistance** in breast cancer cell lines.
AUTHOR: Burchert Andreas(a); Jaenike Manuela(a); Schmidt Manuel; Brendel Cornelia(a); Rieder Harald; Neubauer Andreas(a)
AUTHOR ADDRESS: (a)Hematology/Oncology/Immunology, Philipps-Universitaet, Marburg**Germany
JOURNAL: Blood 98 (11 Part 2):p255b November 16, 2001
MEDIUM: print
CONFERENCE/MEETING: 43rd Annual Meeting of the American Society of Hematology, Part 2 Orlando, Florida, USA December 07-11, 2001
ISSN: 0006-4971
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: STI571 is a novel tyrosine kinase inhibitor with significant activity in BCR-ABL positive leukemias. Response to treatment of patients in blastic phase of chronic myelogenous leukemia, however, is often limited by the emergence of **resistance**. BCR-ABL overexpression and BCR-ABL kinase mutation have been suggested as mechanisms of STI571 **resistance**. In vitro, however, BCR-ABL positive, but STI571 **resistant** cell lines were generated, which did neither display BCR-ABL mutations nor BCR-ABL overexpression, suggesting BCR-Ab1 independent **resistance** mechanisms. Therefore, we postulated that tolerability to STI571 can be the result of an activity of this compound on proteins and pathways unrelated to ABL, BCR-ABL, the platelet derived growth factor receptor (PDGFR), and the stem cell factor receptor (c-kit): In the breast cancer cell lines MDA-MB231, MDA-MB468, and SKBR-3, which lack significant expression of these specific targets, STI571 inhibited proliferation (IC50: 0.3 microM to 15microM) and caused cell dead. Furthermore, it induced a dose dependent paradoxical hyperphosphorylation, but also a dephosphorylation of several proteins, such as **Her-2** and the epidermal growth factor receptor-receptor (EGFR). Through generation of **resistant** derivatives of the STI571-susceptible parental cell lines, we provide evidence that STI571 can induce **resistance** independent from the presence of activated ABL. Interestingly, three of four **resistant** cell lines displayed three to four fold higher **Her-2** levels compared to the parental lines, and **Her-2** over-expression was accompanied by **Her-2** gene amplification in MDA-MB435 cells. We conclude that STI571 has an activity in tumor cell lines, which can result in **resistance** through upregulation of proto-oncogenes. This implies that STI571 **resistance** of BCR-ABL positive leukemias could be the result of selective up-regulation of other oncogenes frequently found in progressed phases of CML and in BCR-ABL positive ALL.

2001

6/3,AB/108 (Item 10 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
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13472234 BIOSIS NO.: 200200101055
Y-box factor YB-1 predicts **drug resistance** and patient outcome in breast cancer independent of clinically relevant tumor biologic factors HER2, uPA and PAI-1.
AUTHOR: Janz Martin; Harbeck Nadia; Dettmar Peer; Berger Ursula; Schmidt Anja; Juerchott Karsten; Schmitt Manfred; Royer Hans-Dieter(a)
AUTHOR ADDRESS: (a)Institut fuer Transplantationsdiagnostik und Zelltherapeutika, Moorenstrasse 5, D-40225, Duesseldorf**Germany E-Mail: hroyer@itz.uni-duesseldorf.de
JOURNAL: International Journal of Cancer 97 (3):p278-282 20 January, 2002
MEDIUM: print
ISSN: 0020-7136
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Intrinsic or acquired **resistance** to chemotherapy is responsible for failure of current treatment regimens in breast cancer patients. The Y-box protein YB-1 regulates expression of the P-glycoprotein gene mdr1, which plays a major role in the development of a multidrug-**resistant** tumor phenotype. In human breast cancer, overexpression and nuclear localization of YB-1 is associated with upregulation of P-glycoprotein. In our pilot study, we analyzed the clinical relevance of YB-1 expression in breast cancer (n=83) after a median follow-up of 61 months and compared it with tumor-biologic factors already used for clinical risk-group discrimination, i.e., HER2, urokinase-type plasminogen activator (uPA) and plasminogen activator inhibitor type 1 (PAI-1). High YB-1 expression in tumor tissue and surrounding benign breast epithelial cells was significantly associated with poor patient outcome. In patients who received postoperative chemotherapy, the 5-year relapse rate was 66% in patients with high YB-1 expression. In contrast, in patients with low YB-1 expressions, no relapse has been observed so far. YB-1 expression thus indicates clinical **drug resistance** in breast cancer. Moreover, YB-1 correlates with breast cancer aggressiveness: in patients not treated with postoperative chemotherapy, those with low YB-1 expression are still free of disease, whereas the 5-year relapse rate in those with high YB-1 was 30%. There was no significant correlation between YB-1 expression and either HER2 expression or uPA and PAI-1 levels. Risk-group assessment achieved by YB-1 differed significantly from that by HER2 or uPA/PAI-1. In conclusion, YB-1 demonstrated prognostic and predictive significance in breast cancer by identifying high-risk patients in both the presence and absence of postoperative chemotherapy, independent of tumor-biologic factors currently available for clinical decision making.

2002

6/3,AB/109 (Item 11 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
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13380310 BIOSIS NO.: 200200009131
Tyrosine kinase inhibitors: Rationale, mechanisms of action, and implications for **drug resistance**.
AUTHOR: Busse Dagmar; Yakes F Michael; Lenferink Anne E G; Arteaga Carlos L (a)
AUTHOR ADDRESS: (a)Division of Oncology, Vanderbilt University School of Medicine, 777 Preston Res. Bldg, Nashville, TN, 37232-6307**USA
JOURNAL: Seminars in Oncology 28 (5 Suppl. 16):p47-55 October, 2001

MEDIUM: print
ISSN: 0093-7754
DOCUMENT TYPE: Literature Review
RECORD TYPE: Citation
LANGUAGE: English
2001

6/3,AB/110 (Item 12 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
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13373235 BIOSIS NO.: 200200002056
In vitro selection and preliminary characterization of HerceptinTM **resistant** human breast carcinoma cells.
AUTHOR: Chan Carmel T(a); Kane Susan E(a)
AUTHOR ADDRESS: (a)City of Hope National Medical Center, Duarte, CA**USA
JOURNAL: Proceedings of the American Association for Cancer Research Annual Meeting 42p930 March, 2001
MEDIUM: print
CONFERENCE/MEETING: 92nd Annual Meeting of the American Association for Cancer Research New Orleans, LA, USA March 24-28, 2001
ISSN: 0197-016X
RECORD TYPE: Citation
LANGUAGE: English
2001

6/3,AB/111 (Item 13 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
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13307718 BIOSIS NO.: 200100514867
HER-2/neu expression in prostate cancer: High level of expression associated with exposure to hormone therapy and androgen independent disease.
AUTHOR: Shi Yan; Brands Frank H; Chatterjee Sunanda; Feng An-Chen; Groshen Susan; Schewe Jorg; Lieskovsky Gary; Cote Richard J(a)
AUTHOR ADDRESS: (a)Department of Pathology, USC/Norris Comprehensive Cancer Center, 1441 Eastlake Ave., Los Angeles, CA, 90033**USA
JOURNAL: Journal of Urology 166 (4):p1514-1519 October, 2001
MEDIUM: print
ISSN: 0022-5347
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English
SUMMARY LANGUAGE: English

ABSTRACT: Purpose: **HER-2/neu** is a proto-oncogene that encodes a transmembrane receptor belonging to the family of epidermal growth factor receptors. Increasing evidences indicates that **HER-2/neu** may contribute to hormone **resistance** in prostate cancer. We investigated **HER-2/neu** expression in primary, androgen dependent and advanced androgen independent prostate cancer, and its potential value as a marker of disease progression. Materials and Methods: Immunohistochemical testing was performed to investigate **HER-2/neu** expression in 81 patients with prostate cancer, including 31 with pathological stage C disease treated with radical prostatectomy without preoperative androgen ablation therapy (untreated group), 30 with pathological stage C disease treated before surgery with androgen ablation therapy (treated group) and 20 with advanced androgen independent prostate cancer (androgen independent group). Tumors were classified based on the percent of tumor cells showing **HER-2/neu** membrane immunoreactivity as low (50%

or less) and high (50% or greater) expression. Results: Of the 31 prostate tumors in the untreated group 9 (29%) showed high **HER-2/neu** expression versus 15 of 30 (50%) in the treated and 17 of 20 (85%) in the androgen independent groups. The difference in **HER-2/neu** expression was significant in the untreated and androgen independent ($p<0.001$) and in the treated and androgen independent ($p=0.016$) groups. There was a significant association of Gleason score with **HER-2/neu** expression in the untreated group ($p=0.038$) but not in the treated group. No association was found of tumor substage with **HER-2/neu** expression. In the untreated group patients with tumors showing high **HER-2/neu** expression had a decreased survival rate ($p=0.044$). Conclusions: High **HER-2/neu** expression is highly associated with exposure to hormone therapy and androgen independence. It may contribute to androgen independence in prostate cancer and identify patients with prostate cancer more likely to have disease progression, particularly those not exposed to previous hormone therapy.

2001

6/3,AB/112 (Item 14 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
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13241654 BIOSIS NO.: 200100448803
Modulation by HER2/**neu** of the cytotoxicity of cisplatin and 1r,2r-diaminocyclohexane-diacetato-dichloro-platinum(IV)(DACH-acetato-Pt) against wild-type p53 MCF-7 breast tumor cells.
AUTHOR: Watanabe M(a); Nakamura J(a); Mujoo K(a); Khokhar A R(a); Siddik Z H(a)
AUTHOR ADDRESS: (a)University of Texas M.D. Anderson Cancer Center, Houston, TX**USA
JOURNAL: Proceedings of the American Association for Cancer Research Annual Meeting 42p425 March, 2001
MEDIUM: print
CONFERENCE/MEETING: 92nd Annual Meeting of the American Association for Cancer Research New Orleans, LA, USA March 24-28, 2001
ISSN: 0197-016X
RECORD TYPE: Citation
LANGUAGE: English
SUMMARY LANGUAGE: English
2001

6/3,AB/113 (Item 15 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
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13159563 BIOSIS NO.: 200100366712
Her2/**neu** induces breast cancer cells **resistance** to all-trans retinoic acid (ATRA) by reducing RARalpha expression.
AUTHOR: Tari Ana M(a); Lim Soo-Jeong(a); Esteva Francisco(a); Zapata Pablo (a); Lopez-Berestein Gabriel(a)
AUTHOR ADDRESS: (a)UT MD Anderson Cancer Center, Houston, TX**USA
JOURNAL: Proceedings of the American Association for Cancer Research Annual Meeting 42p119 March, 2001
MEDIUM: print
CONFERENCE/MEETING: 92nd Annual Meeting of the American Association for Cancer Research New Orleans, LA, USA March 24-28, 2001
ISSN: 0197-016X
RECORD TYPE: Citation
LANGUAGE: English
SUMMARY LANGUAGE: English

2001

6/3,AB/114 (Item 16 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
(c) 2002 BIOSIS. All rts. reserv.

13154697 BIOSIS NO.: 200100361846
Transcription factor YB-1 predicts **drug resistance** and patient prognosis in breast cancer independent of clinically relevant tumor-biological factors HER2, uPA, PAI-1.
AUTHOR: Harbeck Nadia(a); Dettmar Peer; Janz Martin; Berger Ursula; Schmitt Manfred; Royer Hans-Dieter
AUTHOR ADDRESS: (a)Max-Delbrueck Center for Molecular Medicine, Berlin** Germany
JOURNAL: Proceedings of the American Association for Cancer Research Annual Meeting 42p118 March, 2001
MEDIUM: print
CONFERENCE/MEETING: 92nd Annual Meeting of the American Association for Cancer Research New Orleans, LA, USA March 24-28, 2001
ISSN: 0197-016X
RECORD TYPE: Citation
LANGUAGE: English
SUMMARY LANGUAGE: English
2001

6/3,AB/115 (Item 17 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
(c) 2002 BIOSIS. All rts. reserv.

13101791 BIOSIS NO.: 200100308940
Geldanamycin and its analogue 17-allylamino-17-demethoxygeldanamycin (17-AAG) lower Bcr-Abl level and induce apoptosis and differentiation of Bcr-Abl positive human leukemic blasts.
AUTHOR: Ramadevi N(a); O'Bryan Erica(a); Bhalla Kapil N(a)
AUTHOR ADDRESS: (a)Interdisciplinary Oncology Program, Moffitt Cancer Center and Research Institute, University of South Florida, Tampa, FL** USA
JOURNAL: Blood 96 (11 Part 1):p306a November 16, 2000
MEDIUM: print
CONFERENCE/MEETING: 42nd Annual Meeting of the American Society of Hematology San Francisco, California, USA December 01-05, 2000
SPONSOR: American Society of Hematology
ISSN: 0006-4971
RECORD TYPE: Abstract
LANGUAGE: English
SUMMARY LANGUAGE: English

ABSTRACT: Ansamycin antibiotic Geldanamycin (GA), and its less toxic analogue 17-allylamino-17-demothoxygeldanamycin (17-AAG), bind strongly to heat shock protein 90 (Hsp90) and disrupt its chaperone association with protein kinases (v-Src, c-Raf-1, and **Her-2-neu**) and mutant p53, causing their reduced stability and proteasomal degradation. HL-60/Bcr-Abl cells, with ectopic expression of p185 Bcr-Abl tyrosine kinase (TK) and K562 cells (with endogenous expression of p210 Bcr-Abl TK) display a high degree of **resistance** against antileukemic **drug** (i.e., Ara-C and etoposide)-induced apoptosis (Blood 96:2246, 2000). Our present studies demonstrate that exposure to 1.0 to 5.0 muM GA or 17-AAG for 24-72 hours, induces apoptosis of HL-60/neo > HL-60/Bcr-Abl > K562 cells in a dose and time dependent manner. GA or 17-AAG-induced apoptosis was associated with cytosolic accumulation of cyt c and cleavage and activities of caspase-9 and -3. GA or 17-AAG downregulated intracellular Bcr-Abl and c-Raf, but not

IkappaBalpha or Bcl-xL protein levels, as well as reduced the Akt kinase activity in HL-60/Bcr-Abl and K562 cells. Treatment with GA or 17-AAG significantly increased the intracellular levels of Hb in HL-60/Bcr-Abl and K562 cells. while HL-60/neo cells have barely detectable levels, HL-60/Bcr-Abl and K562 cells display approximately 8 to 10-fold higher levels of Hsp70. This was further induced by treatment with 5 muM of GA or 17-AAG for 24 hours, which was associated with GA or 17-AAG-induced apoptosis of HL-60/Bcr-Abl or K562 cells. Similar to Raf-1, Bcr-Abl TK has chaperone-association with Hsp90. Immunoprecipitation with anti-Bcr or anti-Abl antibody followed by immunoblotting with anti-Hsp90 or Hsp70 antibody, demonstrated that GA or 17-AAG treatment shifted the binding of Bcr-Abl from Hsp90 to Hsp70. GA and 17-AAG induced the proteasomal degradation of Bcr-Abl, suggested by the observation that co-treatment with proteasome inhibitor PSC341 reduced both GA (or 17-AAG) mediated downregulation of Bcr-Abl levels and inhibited apoptosis of HL-60/Bcr-Abl and K562 cells. These data show that by disrupting the binding of Hsp90 with Bcr-Abl, GA or 17-AAG induces its proteasomal degradation, thereby promoting the intrinsic or mitochondrial pathway of apoptosis in Bcr-Abl positive leukemic cells. These results support the in vivo investigation of 17-AAG against Bcr-Abl positive leukemias.

2000

6/3,AB/116 (Item 18 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
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13048888 BIOSIS NO.: 200100256037
Loss of anchorage-independent growth and reduced invasiveness in multidrug **resistant** breast cancer cells and its relationship to expression of p66-Shc and caveolin-1.
AUTHOR: Fiucci Giusy(a); Ravid Dana(a); Reich Reuven; Liscovitch Mordechai (a)
AUTHOR ADDRESS: (a)Weizmann Institute of Science, Jerusalem**Israel
JOURNAL: FASEB Journal 15 (4):pA209 March 7, 2001
MEDIUM: print
CONFERENCE/MEETING: Annual Meeting of the Federation of American Societies for Experimental Biology on Experimental Biology 2001 Orlando, Florida, USA March 31-April 04, 2001
ISSN: 0892-6638
RECORD TYPE: Abstract
LANGUAGE: English
SUMMARY LANGUAGE: English

ABSTRACT: Multidrug **resistance** of cancer cells is associated with up-regulation of caveolin expression and elevated surface density of caveolae, but the functional impact of these changes on regulation of MDR cell growth and invasiveness are unknown. Caveolin-1 inhibits growth factor activation of the extracellular signal-regulated kinase (ERK) pathway, but also recruits the adaptor protein Shc to an a-integrin-associated complex, leading to integrin-dependent activation of ERK. Here we report that the 66-kDa isoform of Shc (p66-Shc) is highly expressed in multidrug **resistant** MCF-7/AdrR human mammary adenocarcinoma cells, along with the more common isoforms, p46-Shc and p52-Shc, that are expressed in **drug**-sensitive MCF-7 cells. ERK1 and ERK2 exhibit high basal activity in quiescent MCF-7/AdrR cells, whereas **Neu** differentiation factor (NDF)-induced activation of ERK1 and ERK2 is attenuated. ERK activation is decreased also in caveolin-1-transfected MCF-7 cells. p66-Shc is localized in part in low density, caveolin-rich membrane domains prepared from MCF-7/AdrR cells. Co-immunoprecipitation experiments indicate that in adherent MCF-7/AdrR cells p66-Shc is constitutively associated with caveolin-1 and that caveolin-1 and p66-Shc are associated with ErbB2 in an NDF-independent

manner. However, the p66-Shc-caveolin complex is dissociated upon cell detachment, indicating that its formation depends on cell interaction with the extracellular matrix. Whereas MCF-7 cells readily from colonies in soft agar, MCF-7/AdrR cells are largely incapable of anchorage-independent growth and exhibit reduced invasive capacity and matrix metalloprotease-2 release. Expression of recombinant caveolin-1 in MCF-7 cells elicits similar effects. We conclude that the high expression levels of caveolin-1 and possibly p66-Shc found in MCF-7/AdrR cells exert a negative modulatory effect on growth factor-induced ERK activation and reverses two important aspects of transformation, namely, anchorage-independent growth and invasiveness.

2001

6/3,AB/117 (Item 19 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
(c) 2002 BIOSIS. All rts. reserv.

12905552 BIOSIS NO.: 200100112701
Akt2 upregulation in **HER-2/neu** overexpressing breast cancers: Implications to their clinical and biological behavior.
AUTHOR: Bacus S(a); Esteva F; Hortobagyi G; Gudkov A
AUTHOR ADDRESS: (a)Quantitative Diagnostics Lab., Elmhurst, IL**USA
JOURNAL: Laboratory Investigation 81 (1):p20A January, 2001
MEDIUM: print
CONFERENCE/MEETING: Annual Meeting of the United States and Canadian Academy of Pathology Atlanta, Georgia, USA March 03-09, 2001
ISSN: 0023-6837
RECORD TYPE: Citation
LANGUAGE: English
SUMMARY LANGUAGE: English
2001

6/3,AB/118 (Item 20 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
(c) 2002 BIOSIS. All rts. reserv.

12899550 BIOSIS NO.: 200100106699
Clinical-pathologic assessment of the clinical sensitivity to single agent taxane (T) therapy for metastatic breast cancer (MBC).
AUTHOR: Van Poznak C(a); Tan L(a); Panageas K(a); Arroyo C(a); Hudis C(a); Norton L(a); Seidman A D(a)
AUTHOR ADDRESS: (a)Memorial Sloan Kettering Cancer Center, New York, NY** USA
JOURNAL: Breast Cancer Research and Treatment 64 (1):p76 November, 2000
MEDIUM: print
CONFERENCE/MEETING: 23rd Annual San Antonio Breast Cancer Symposium San antonio, Texas, USA December 06-09, 2000
ISSN: 0167-6806
RECORD TYPE: Citation
LANGUAGE: English
SUMMARY LANGUAGE: English
2000

6/3,AB/119 (Item 21 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
(c) 2002 BIOSIS. All rts. reserv.

12882561 BIOSIS NO.: 200100089710
Prospective study of signal transduction pathways associated with response and **resistance** to Herceptin(R)-based therapy for patients with

metastatic breast cancer.
AUTHOR: Bacus S S(a); Hortobagyi G; Esteva F J
AUTHOR ADDRESS: (a)Quantitative Diagnostics Laboratory, Elmhurst, IL**USA
JOURNAL: Breast Cancer Research and Treatment 64 (1):p135 November, 2000
MEDIUM: print
CONFERENCE/MEETING: 23rd Annual San Antonio Breast Cancer Symposium San antonio, Texas, USA December 06-09, 2000
ISSN: 0167-6806
RECORD TYPE: Citation
LANGUAGE: English
SUMMARY LANGUAGE: English
2000

6/3,AB/120 (Item 22 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
(c) 2002 BIOSIS. All rts. reserv.

12820698 BIOSIS NO.: 200100027847
Low **HER 2/NEU** gene expression is associated with pathological response to primary paclitaxel and radiation in locally advanced breast cancer (LABC).
AUTHOR: Formenti S C(a); Groshen S; Florentine B; Park M J; Danenberg P V
AUTHOR ADDRESS: (a)New York University, New York, NY**USA
JOURNAL: International Journal of Radiation Oncology Biology Physics 48 (3 Supplement):p143 2000
MEDIUM: print
CONFERENCE/MEETING: 42nd Annual Meeting of the American Society for Therapeutic Radiology and Oncology Boston, Massachusets, USA October 22-26, 2000
SPONSOR: American Society for Therapeutic Radiology and Oncology
ISSN: 0360-3016
RECORD TYPE: Citation
LANGUAGE: English
SUMMARY LANGUAGE: English
2000

6/3,AB/121 (Item 23 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
(c) 2002 BIOSIS. All rts. reserv.

12707937 BIOSIS NO.: 200000461439
Molecular analysis and therapeutic application; molecular targeting for breast cancer treatment.
AUTHOR: Tani Yoichi(a)
AUTHOR ADDRESS: (a)DAKO Lab, DAKO Japan Co., Ltd., Nishinotouin-higashiiru, Shijo-dori, Shimogyo-ku, Kyoto, 600-8493**Japan
JOURNAL: Acta Histochemica et Cytochemica 33 (3):p185-188 2000
MEDIUM: print
ISSN: 0044-5991
DOCUMENT TYPE: Literature Review
RECORD TYPE: Abstract
LANGUAGE: English
SUMMARY LANGUAGE: English

ABSTRACT: Advanced biotechnologies have provided benefits to detect a variety of cellular molecules for tumor diagnosis, determination of malignancy, and prognosis of cancers. Improved understanding of the molecular basis of cancers will lead to molecular targeted approaches to cancer prevention and treatment. Monoclonal antibody-based therapeutics targeting cell surface receptor such as HER2/**neu**/c-erbB2 oncoprotein on breast cancer cells has shown efficacy in clinical trials. HER2 pro-oncogene is a member of the epidermal growth factor receptor

family, and HER2 oncoprotein is a well-characterized predictor of tumor aggressiveness. The overexpression of HER2 has been found in about 25% to 30% of breast cancers and associated with poor prognosis, **resistance** to hormonal therapy and lack of sensitivity to some adjuvant chemotherapy. The recombinant anti-HER2 monoclonal antibody, trastsuzumab (Herceptin), was evaluated in clinical trials for treatment of HER2-overexpressing metastatic breast cancers. The administration of the trastuzumab has produced an objective response in patients with metastatic breast cancers, suggesting that the trastuzumab will be a new molecular targeting therapeutic agent for patients with HER2-overexpressing cancer. Thus, a test result of HER2 overexpression will be a valid criterion in determining eligibility for the trastsuzumab therapy, and reliable detection of HER2 overexpression is an important prerequisite for the success of the trastsuzumab therapy.

2000

6/3,AB/122 (Item 24 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
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12653774 BIOSIS NO.: 200000407276
Biomarker conservation in primary and metastatic epithelial ovarian cancer.
AUTHOR: Tewari Krishnansu Sujata; Kyshtoobayeva Ainura S; Mehta Rita S; Yu Ing-Ru; Burger Robert A; DiSaia Philip J; Fruehauf John P(a)
AUTHOR ADDRESS: (a)Oncotech, Inc., 1791 Kaiser Ave., Irvine, CA**USA
JOURNAL: Gynecologic Oncology 78 (2):p130-136 August, 2000
MEDIUM: print
ISSN: 0090-8258
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English
SUMMARY LANGUAGE: English

ABSTRACT: Purpose: The aim of this study was to compare the overexpression of specific biomarkers in primary advanced and recurrent epithelial ovarian cancers. Methods: Biomarker expression by epithelial ovarian cancer specimens from primary and metastatic sites was examined by immunohistochemistry and flow cytometry. Biomarker expression by subpopulations of tissues consisting of matched pairs of synchronous and metachronous lesions was also studied. Results: A total of 3173 epithelial ovarian cancer specimens were retrieved from women with FIGO Stage III/IV disease. These included lesions from 1036 primary and 2137 metastatic sites. The percentages of biomarker expression for primary and metastatic lesions, respectively, were MDR1, 12 and 10%; p53, 55 and 60%; HER2, 12 and 11%; EGF-R, 26 and 33%; increased microvessel counts (CD31), 21 and 36%. Approximately 73% of both primary and metastatic specimens were aneuploid, and approximately 57% of both sets had an S-phase fraction >7%. Only EGF-R and CD31 expression were found to be significantly different between the primary and metastatic tumors ($P < 0.05$). Of the paired synchronous cases ($n = 48$) evaluated, 88% of aneuploid primary lesions were associated with aneuploid metastases. Similarly, the distributions for MDR1, HER2, and p53 expression did not vary significantly between primary and metastatic sites. Pairings of metachronous cases ($n = 66$) revealed that nearly 80% of primary aneuploid tumors ($n = 39$) retained their aneuploid status at the time of relapse. Furthermore, there were no significant changes in MDR1, p53, or HER2 expression at relapse. Conclusions: With the exception of EGF-R and CD31, clonal divergence of the biomarkers evaluated in this study probably does not play a significant role in imparting clinical heterogeneity during the advanced and recurrent stages of epithelial ovarian cancer. These particular genes likely undergo alterations early in the tumorigenesis process before metastases have become established.

2000

6/3,AB/123 (Item 25 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
(c) 2002 BIOSIS. All rts. reserv.

12619772 BIOSIS NO.: 200000373274
Compositions and methods for reducing radiation and **drug resistance** in cells.
AUTHOR: Chang Esther H(a); Pirollo Kathleen F
AUTHOR ADDRESS: (a)7508 Vale St., Chevy Chase, MD, 20815**USA
JOURNAL: Official Gazette of the United States Patent and Trademark Office Patents 1231 (4):pNo pagination Feb. 22, 2000
MEDIUM: e-file
ISSN: 0098-1133
DOCUMENT TYPE: Patent
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Provided are antisense oligonucleotides directed against the raf-1 gene, Ha-ras gene and **HER-2** gene, components of a signal transduction pathway involving oncogenes and their normal counterparts and leading to the phenotype of cellular radioresistance. Administration of these antisense oligonucleotides is shown to reverse the radioresistance phenotype in cells overexpressing **HER-2** or a mutant form of Ha-ras. Methods and compositions for reversing radiation **resistance** among other conditions involving these genes are disclosed.

2000

6/3,AB/124 (Item 26 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
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12541170 BIOSIS NO.: 200000294672
Anti-HER2 antibody enhances the growth inhibitory effect of anti-oestrogen on breast cancer cells expressing both oestrogen receptors and HER2.
AUTHOR: Kunisue H; Kurebayashi J; Otsuki T; Tang C K; Kurosumi M; Yamamoto S; Tanaka K; Doihara H; Shimizu N; Sonoo H
AUTHOR ADDRESS: (a)Department of Breast and Thyroid Surgery, Kawasaki Medical School, 577 Matsushima Kurashiki, Okayama, 701-0192**Japan
JOURNAL: British Journal of Cancer 82 (1):p46-51 Jan., 2000
MEDIUM: print.
ISSN: 0007-0920
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English
SUMMARY LANGUAGE: English

ABSTRACT: Anti-oestrogen is effective for the treatment of oestrogen receptor (ER)-positive breast carcinomas, but most of these tumours become **resistant** to anti-oestrogen. It has been suggested that anti-oestrogen therapy may induce a HER2 signalling pathway in breast cancer cells and this may cause **resistance** to anti-oestrogen. Thus, it is conceivable that combined therapy with anti-oestrogen and anti-HER2 antibody might be more effective. In the present study, we investigated the effect of combined treatment with a humanized anti-HER2 monoclonal antibody, rhumAbHER2 (trastuzumab), and an anti-oestrogen, ICI 182,780, on the cell growth of three human breast cancer cell lines which respectively express different levels of ER and HER2. The combined treatment enhanced the growth inhibitory effect on ML-20 cells, which

express a high level of ER and a moderate level of HER2, but showed no additive effect on either KPL-4 cells, which express no ER and a moderate level of HER2, or MDA-MB-231 cells, which express no ER and a low level of HER2. It is also suggested that both the antibody and anti-oestrogen induce a G1-S blockade and apoptosis. These findings indicate that combined treatment with anti-HER2 antibody, and anti-oestrogen may be useful for the treatment of patients with breast cancer expressing both ER and HER2.

2000

6/3,AB/125 (Item 27 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
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12522028 BIOSIS NO.: 200000275530
Effects of **HER-2** expression levels on **drug resistance** of breast and ovarian cancer cells.
AUTHOR: Aigner Achim(a); Hsieh Susie S; Malerczyk Claudius; Wuestenhagen Andrea; Butscheid Moritz; Apel Juergen; Czubayko Frank
AUTHOR ADDRESS: (a)CV Res Eli Lilly, Indianapolis, IN**USA
JOURNAL: Proceedings of the American Association for Cancer Research Annual Meeting (41):p765 March, 2000
MEDIUM: print.
CONFERENCE/MEETING: 91st Annual Meeting of the American Association for Cancer Research. San Francisco, California, USA April 01-05, 2000
ISSN: 0197-016X
RECORD TYPE: Citation
LANGUAGE: English
SUMMARY LANGUAGE: English
2000

6/3,AB/126 (Item 28 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
(c) 2002 BIOSIS. All rts. reserv.

12516832 BIOSIS NO.: 200000270334
Effect of **HER-2/neu** on the promoter activity of human MDR1 gene.
AUTHOR: Yang J M(a); Vassil Andrew(a); Hait W N(a)
AUTHOR ADDRESS: (a)UMDNJ-Robert Wood Johnson Med Sch, New Brunswick, NJ** USA
JOURNAL: Proceedings of the American Association for Cancer Research Annual Meeting (41):p782 March, 2000
MEDIUM: print.
CONFERENCE/MEETING: 91st Annual Meeting of the American Association for Cancer Research. San Francisco, California, USA April 01-05, 2000
ISSN: 0197-016X
RECORD TYPE: Citation
LANGUAGE: English
SUMMARY LANGUAGE: English
2000

6/3,AB/127 (Item 29 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
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12485078 BIOSIS NO.: 200000238580
Comparative efficacy of an anti-sense oligonucleotide to **HER-2/neu** in combination with Tamoxifen versus HerceptinTM and Tamoxifen in **HER-2/neu** overexpressing human breast tumor cell

lines.
AUTHOR: Chia Stephen K L(a); Gelmon K(a); Saxon D(a); Bally M(a)
AUTHOR ADDRESS: (a)British Columbia Cancer Agency, Vancouver, BC**Canada
JOURNAL: Proceedings of the American Association for Cancer Research Annual Meeting (41):p389 March, 2000
CONFERENCE/MEETING: 91st Annual Meeting of the American Association for Cancer Research. San Francisco, California, USA April 01-05, 2000
ISSN: 0197-016X
RECORD TYPE: Citation
LANGUAGE: English
SUMMARY LANGUAGE: English
2000

6/3,AB/128 (Item 30 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
(c) 2002 BIOSIS. All rts. reserv.

12484637 BIOSIS NO.: 200000238139
Cell-cycle dysregulation and the molecular mechanisms of prostate cancer.
AUTHOR: Amanatullah Derek F(a); Reutens Anne T(a); Zafonte Brian T(a); Fu Maofu(a); Mani Sridhar(a); Pestell Richard G(a)
AUTHOR ADDRESS: (a)Albert Einstein Cancer Center, Albert Einstein College of Medicine, 1300 Morris Park Ave., Bronx, NY, 10461**USA
JOURNAL: Frontiers in Bioscience 5 (CITED APRIL 12, 2000):pd372-390 Jan. 1- April 1, 2000
DOCUMENT TYPE: Literature Review
RECORD TYPE: Abstract
LANGUAGE: English
SUMMARY LANGUAGE: English

ABSTRACT: Prostate cancer is the most common cause of non-cutaneous cancer in men and although frequently latent is the second commonest cause of death. Screening for the disease was historically based on symptoms of urethral obstruction, clinical examination of the prostate gland and serum measurements of prostate specific antigen. As prostate cancer growth in the early stages is enhanced by androgens, the mainstay of therapy has been androgen ablation by pharmaco-therapeutic or surgical means. The subsequent development of androgen therapy **resistant** prostate cancer in many patients, for whom therapeutic options remain limited, has led researchers to focus attention on understanding the molecular genetics of prostate cancer. The array of genetic abnormalities observed in prostate tumors, which include changes in components of the cell cycle, suggest the disease is quite heterogeneous and may require further sub-classification based on genetic markers. Such analyses may lead to identification of relevant new prognostic and therapeutic indicators. The advent of transgenic mouse models of prostate cancer may provide a critical tool for the implementation of rational genetic based therapeutics and alternate **drug** design.

2000

6/3,AB/129 (Item 31 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
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12395886 BIOSIS NO.: 200000149388
Elevated serum **her-2/neu** predicts **resistance** to megace but not to an aromatase inhibitor.
AUTHOR: Ali SM(a); Leitzel KE; Chinchilli V; Engle L; Demers L; Carney W; Allard J; Cook G; Lassus M; Brady C; Lipton A
AUTHOR ADDRESS: (a)Penn State Univ., Hershey, PA, 17033**USA
JOURNAL: Breast Cancer Research and Treatment. 57 (1):p62 1999

CONFERENCE/MEETING: 22nd Annual San Antonio Breast Cancer Symposium San Antonio, Texas, USA December 8-11, 1999
ISSN: 0167-6806
RECORD TYPE: Citation
LANGUAGE: English
SUMMARY LANGUAGE: English
1999

6/3,AB/130 (Item 32 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
(c) 2002 BIOSIS. All rts. reserv.

11933159 BIOSIS NO.: 199900179268
Predictive factors for local recurrence and distant metastasis of breast cancer after lumpectomy with postoperative radiation therapy.
AUTHOR: Bui M M; Amornmarn R; Prempree T; Masood S
AUTHOR ADDRESS: Univ. Florida Health Sci. Center, Jacksonville, FL 32209** USA
JOURNAL: Proceedings of the American Association for Cancer Research Annual Meeting 40p495 March, 1999
CONFERENCE/MEETING: 90th Annual Meeting of the American Association for Cancer Research Philadelphia, Pennsylvania, USA April 10-14, 1999
SPONSOR: American Association for Cancer Research
ISSN: 0197-016X
RECORD TYPE: Citation
LANGUAGE: English
1999

6/3,AB/131 (Item 33 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
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11929886 BIOSIS NO.: 199900175995
Natural expression of ErbB2 (**her-2/neu**) during the development of normal rat mammary epithelial cells.
AUTHOR: Darcy K M; Zangani D; Wohlhueter A L; Vaughan M M; Russell J A; Ip M M
AUTHOR ADDRESS: Roswell Park Cancer Inst., Buffalo, NY 14263**USA
JOURNAL: Proceedings of the American Association for Cancer Research Annual Meeting 40p636 March, 1999
CONFERENCE/MEETING: 90th Annual Meeting of the American Association for Cancer Research Philadelphia, Pennsylvania, USA April 10-14, 1999
SPONSOR: American Association for Cancer Research
ISSN: 0197-016X
RECORD TYPE: Citation
LANGUAGE: English
1999

6/3,AB/132 (Item 34 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
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11788339 BIOSIS NO.: 199900034448
The **HER-2/neu** oncogene in breast cancer: Prognostic factor, predictive factor, and target for therapy.
AUTHOR: Ross Jeffrey(a); Fletcher Jonathan A
AUTHOR ADDRESS: (a)Dep. Pathol., Albany Med. Coll., Mail Code 81, 47 New Scotland Ave., Albany, NY 12208**USA
JOURNAL: Stem Cells (Miamisburg) 16 (6):p413-428 1998
ISSN: 1066-5099
DOCUMENT TYPE: Article

RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: The **HER-2/neu** oncogene encodes a transmembrane tyrosine kinase receptor with extensive homology to the epidermal growth factor receptor. **HER-2/neu** has been widely studied in breast cancer. In this review, the association of **HER-2/neu** gene and protein abnormalities studied by Southern and slot blotting, immunohistochemistry, enzyme immunoassays, and fluorescence in situ hybridization with prognosis in breast cancer is studied in depth by review of a series of 47 published studies encompassing more than 15,000 patients. The relative advantages of gene amplification assays and frozen/fresh tissue immunohistochemistry over paraffin section immunohistochemistry are discussed. The significance of **HER-2/neu** overexpression in ductal carcinoma in situ and the **HER-2/neu** status in uncommon female breast conditions and male breast cancer are also considered. The potential value of **HER-2/neu** status for the prediction of response to therapy in breast cancer is presented in the light of a series of recently published studies showing a range of impact on the outcome of patients treated with hormonal, cytotoxic, and radiation therapies. The evidence that **HER-2/neu** gene and protein abnormalities in breast cancer predict **resistance** to tamoxifen therapy and relative sensitivity to chemotherapy regimens including adriamycin is presented. The review will also evaluate the status of serum-based testing for circulating the **HER-2/neu** receptor protein and its ability to predict disease outcome and therapy response. In the final section, the review will briefly present preliminary data concerning the use of antibody-based therapies directed against the **HER-2/neu** protein and their potential to become a new modality for breast cancer treatment. The recently presented phase III clinical trial evidence that systemic administration of anti-HER2 antibodies (Herceptin), alone and in combination with cytotoxic chemotherapy in patients with **HER-2/neu** overexpressing primary tumors, can increase the time to recurrence and overall response rates in metastatic breast cancer is reviewed.

1998

6/3,AB/133 (Item 35 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
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11413644 BIOSIS NO.: 199800194976
Correlation of nucleotide excision repair (NER) with cisplatin (CDDP) cytotoxicity and with expression of epidermal growth factor receptor (EGFR) and **HER-2/neu** in non-small cell lung cancer (NSCLC) cells.
AUTHOR: Tsai C M(a); Chang K T; Perng R P; Yang L Y
AUTHOR ADDRESS: (a)Chest Dep., Veterans General Hosp., Taipei 11217**Taiwan
JOURNAL: Proceedings of the American Association for Cancer Research Annual Meeting 39p162 March, 1998
CONFERENCE/MEETING: 89th Annual Meeting of the American Association for Cancer Research New Orleans, Louisiana, USA March 28-April 1, 1998
SPONSOR: American Association for Cancer Research
ISSN: 0197-016X
RECORD TYPE: Citation
LANGUAGE: English
1998

6/3,AB/134 (Item 36 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

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11288636 BIOSIS NO.: 199800069968
Resistance of tumor cell lines to killing by tumor necrosis factor-alpha is reduced by an inhibitor of her family tyrosine kinases.
AUTHOR: Le T T; Strawn L M; Powell T J
AUTHOR ADDRESS: Sugen Inc., Redwood City, CA 94063**USA
JOURNAL: Breast Cancer Research and Treatment 46 (1):p113 Oct., 1997
CONFERENCE/MEETING: 20th Annual San Antonio Breast Cancer Symposium San Antonio, Texas, USA December 3-6, 1997
ISSN: 0167-6806
RECORD TYPE: Citation
LANGUAGE: English
1997

6/3,AB/135 (Item 37 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
(c) 2002 BIOSIS. All rts. reserv.

11168177 BIOSIS NO.: 199799789322
Cellular **drug resistance** in lung cancer.
AUTHOR: Krajnik G; Huber H; Pirker R
AUTHOR ADDRESS: Abteilung Klinische Onkol., Universitats-klinik Innere Medizin I, Wien**Austria
JOURNAL: Onkologie 20 (4):p310-314 1997
ISSN: 0378-584X
DOCUMENT TYPE: Literature Review
RECORD TYPE: Abstract
LANGUAGE: English
SUMMARY LANGUAGE: English; German

ABSTRACT: **Drug resistance** limits the clinical efficacy of anticancer drugs in lung cancer which frequently shows intrinsic (non-small-cell lung cancer) or acquired (small-cell lung cancer) **drug resistance**. Several mechanisms of **drug resistance** are present in lung cancer cells. The expression of the MDR1 gene occurs to various degrees. The multidrug **resistance** -associated protein is also present in lung cancer cells. Enhanced activities of glutathione S-transferases and elevated glutathione levels of tumor cells may contribute to the intrinsic **resistance** of non-small-cell lung cancer. Alterations in topoisomerase II activity may also be involved in **drug resistance**. More recently, expression of the **HER-2/neu** oncogene or mutations of the p53 tumor suppressor gene were found to be associated with **drug resistance**, and gene therapy trials with transfer of wild-type p53 into lung cancer cells have been initiated. Thus, **drug resistance** in lung cancer is a complex phenomenon involving several mechanisms although their quantitative contribution to clinical **drug resistance** remains to be determined. Only knowledge of all clinically relevant **drug resistance** mechanisms might eventually lead to new treatment strategies and, thereby, improve the outcome of chemotherapy in lung cancer patients.

1997

6/3,AB/136 (Item 38 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
(c) 2002 BIOSIS. All rts. reserv.

10853655 BIOSIS NO.: 199799474800
The ErbB 2 oncogene and chemotherapy: A mini-review.
AUTHOR: Torre E A; Salimbeni V; Fulco R A(a)

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ABSTRACT: The erbB 2 gene, also known as **Her-2/neu**, is an oncogene that encodes a transmembrane glycoprotein receptor. When overexpressed erbB 2 is an indicator of poor prognosis in a number of cancers. Recent studies show that erbB 2 expression plays a role in the prediction of responsiveness to adjuvant treatment: tumors that had an overexpression of the oncogene were less responsive to treatment than those with a normal amount. Some studies on this oncogene have examined the production of anti-erbB 2 monoclonal antibodies and evaluated the combined effect of monoclonal antibody and chemotherapeutics.